Enantioselective Transformations Promoted by Cooperative Functions of an Achiral Lewis Acid and a Chiral Lewis Acid

Min Cao

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Min Cao

Advisor: Professor Masayuki Wasa

Abstract

This dissertation describes the development of cooperative catalyst systems that contain an achiral Lewis acid and a chiral Lewis acid that may have overlapping functions but play their independent roles to promote enantioselective C–C bond formations. Chapter 1 provides a summary of recent advances made in the field of enantioselective cooperative catalysis that served as intellectual foundations for this dissertation research. As it will be discussed in the first chapter, key limitations of cooperative catalysis are: (1) undesirable catalyst deactivation which occurs due to acid/base complexation, (2) requirement for base sensitive pronucleophiles and acid sensitive electrophiles, and (3) poor reaction efficiency. In an effort to overcome these fundamental limitations, we have developed "frustrated" Lewis pair (FLP)-based catalyst systems that consist of potent and sterically encumbered Lewis acids used in pair with bulky N-containing Lewis bases. To demonstrate the potential of the novel FLP catalyst system, we describe our work involving the enantioselective Conia-ene-type cyclization (Chapter 2). In the subsequent chapter (Chapter 3), we discuss the application of the FLP catalysts for enantioselective β-amino C–H functionalization reactions.

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Chapter One

Recent Advances in Enantioselective Transformations Promoted by Cooperative Catalysts

Introduction

Enantioselective cooperative catalysis[1-2] involves the use of two or more catalyst units (Scheme 1.1) that work in concert to produce chiral organic molecules that cannot be readily synthesized using a single acid or base catalyst.[3] Cooperative functions of the catalysts allow for in situ generation of both nucleophilic and electrophilic partners from otherwise unreactive combination of substrates. Such substrate activation strategy has often been accomplished using bifunctional catalysts[4] (e.g, **C4**, **C5**, **C8**, **C11**; Scheme 1.1) in which the acidic and/or basic moieties are tethered by appropriate linkers. A representative example is the enantioselective

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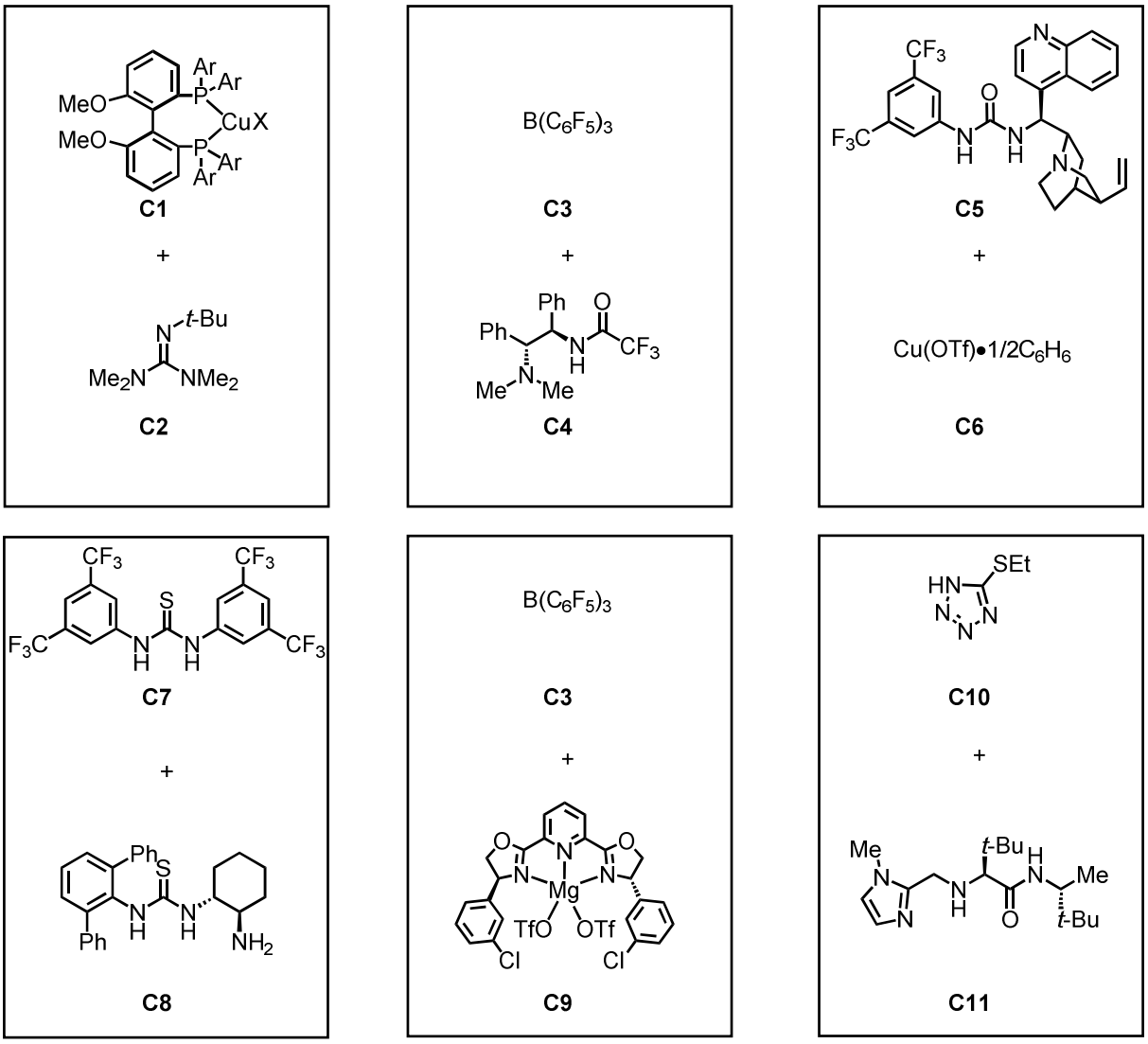
[1] For selected reviews on enantioselective cooperative catalysis, see: (a) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924−1942. (b) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626−2704. (c) Allen, A. E.; MacMillan, D. W. *Chem. Sci*. **2012**, *3*, 633−658. (d) Trost, B. M.; Bartlett, M. J. *Acc. Chem. Res.* **2015**, *48*, 688−701. (e) Shibasaki, M.; Kumagai, N. in *Cooperative Catalysis: Designing Efficient Catalysts for Synthesis*, Peters, R., Eds.; Wiley-VCH: New York, 2015; Chapter 1. (f) Lu, X.; Deng, L. in *Cooperative Catalysis: Designing Efficient Catalysts for Synthesis*, Peters, R., Eds.; Wiley-VCH: New York, 2015; Chapter 5. (g) Inamdar, S. M.; Shinde, V. S.; Patil, N. T. *Org. Biomol. Chem.,* **2015**, *13*, 8116−8162. (h) Wang, M. H.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2016**, *55*, 14912−14922. (i) Romiti, F.; del Pozo, J.; Paioti, P. H. S.; Gonsales, S. A.; Li, X.; Hartrampf, F. W. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2019**, *141*, 17952−17961. (j) Sancheti, S. P.; Urvashi, Shah, M. P.; Patil, N. T. *ACS Catal.* **2020***, 10*, 3462-3489.

[2] For selected reviews on enantioselective non-covalent catalysis, see: (a) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656−5682. (b) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222−4266. (c) Adair, G.; Mukherjee, S.; List, B. *Aldrichimica Acta* **2008**, *41*, 31−39. (d) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187−1198. (e) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603−614. (f) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534−561. (g) Neel, A. J.; Hilton, M. J.; Sigman, M. S.; Toste, F. D. *Nature* **2017**, *543,* 637−646.

[3] For selected reports on enantioselective cooperative catalysis, see: (a) Yang, T.; Ferrali, A.; Sladojevich, F.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 9140−9141. (b) Burns, N. Z.; Witten, M. R.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2011**, *133*, 14578−14581. (c) Manville, N.; Alite, H.; Haeffner, F.; Hoveyda, A. H.; Snapper, M. L. *Nat. Chem.* **2013**, *5*, 768−774. (d) Yin, L.; Brewitz. L.; Kumagai, N.; Shibasakl, M. *J. Am. Chem. Soc*. **2014**, *136*, 17958−17961. (e) Shang, M.; Wang, X.; Koo, S. M.; Youn, J.; Chan, J. Z.; Yao, W.; Hastings, B. T.; Wasa, M. *J. Am. Chem. Soc.* **2017**, *139*, 95−98. (f) Shang, M.; Cao, M.; Wang, Q.; Wasa, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 13338−13526. (g) Shang, M.; Chan, J. Z.; Cao, M.; Chang, Y.; Wang, Q.; Cook, B.; Torker, S.; Wasa, M. *J. Am. Chem. Soc.* **2018**, *140*, 10593−10601. (h) Chan, J. Z.; Yesilcimen, A.; Cao, M.; Zhang, Y.; Zhang, B. C.; Wasa, M. *J. Am*. *Chem*. *Soc*. **2020**, *142*, 16493−16505.

[4] (a) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett **2005**, 10*, 1491−1508. (b) Paull, D. H.; Abraham, C. J.; Scerba, M. T.; Alden-Danforth, E.; Lectka, T. *Acc. Chem. Res.* **2008**, *41*, 655−633. (c) Dixon, Darren J. *Beilstein J. Org. Chem*. **2016**, *12*, 1079–1080.

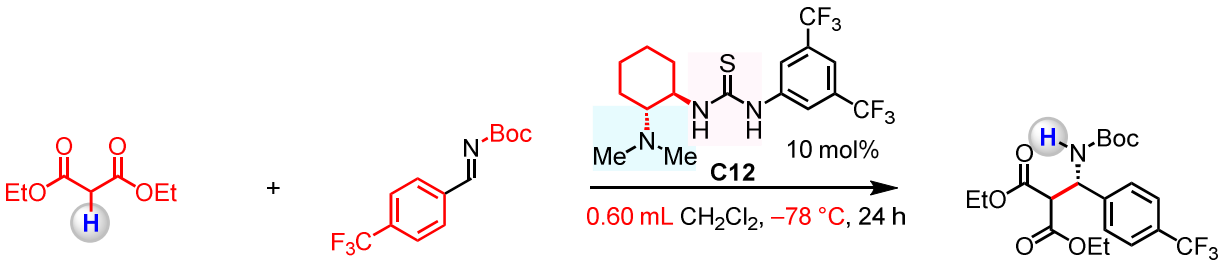
Scheme 1.1. Enantioselective Cooperative Catalysts



Mannich-type reaction which occurs in between a 1,3-dicarbonyl compound **1.1** and an aldimine **1.2** and is promoted by a chiral amino thiourea catalyst **C12** (Scheme 1.2).[5] As can be seen in this example, one distinct advantage of bifunctional catalysis is that catalyst deactivation through undesirable acid/base complexation (e.g., between the H-bond donors and tertiary amine unit of

[5] Yamaoka, Y.; Miyabe, H.; Yasui, Y.; Takemoto, Y. *Synthesis* **2007**, *16*, 2571–2575.

Scheme 1.2. Enantioselective Mannich-Type Reaction Promoted by an Amino-thiourea Catalyst



general advanatges:
circumvents mutual quenching proximity effect

unresolved problems:
cumbersome catalyst synthesis/optimization
demand highly acid/base senstive substrates
difficult to supress racemic background reaction

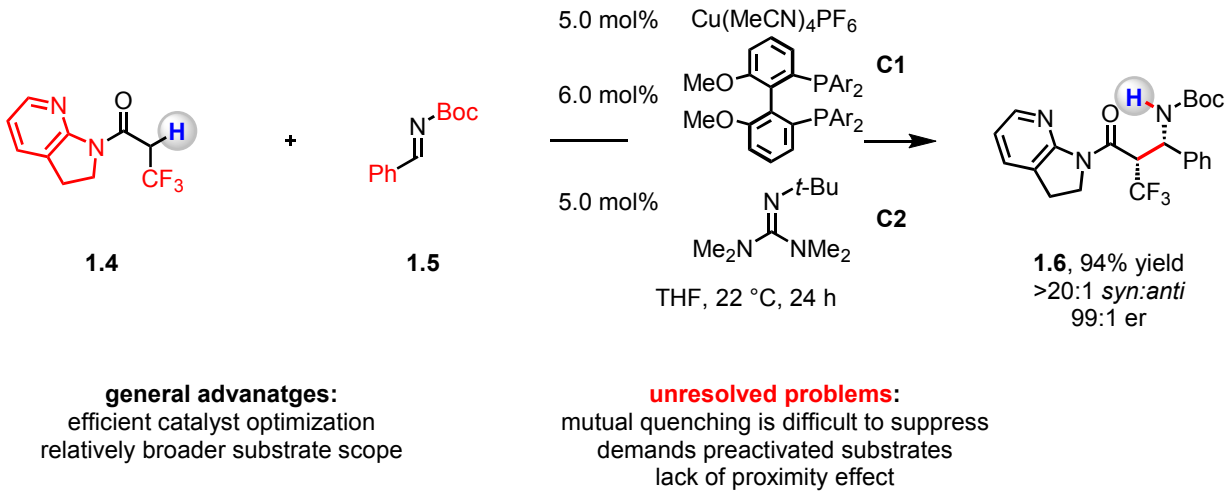
C12) can be circumvented because the catalyst units are geometrically fixed. Such structural rigidity translates to acceleration of the desirable transformation as the catalyst-bound reaction partners can be proximately positioned within the catalyst framework (i.e., proximity effect).[6] Despite these notable advantages, bifunctional catalysis has several key shortcomings. Firstly, synthesis of the bifunctional catalysts through tethering of the acidic and basic entities is often cumbersome, thereby making their evaluation and optimization to be inefficient. Moreover, substrates that undergo efficient reactions are typically contrived to those that are small in size and/or those that have electronic affinities with the catalyst's activation site; those that are sterically hindered and/or possess functional groups that are electronically repulsive against the catalyst are often incompatible. Furthermore, bifunctional catalysts are not immune to intermolecular acid/base complexation.[4] To avoid such unwanted catalyst deactivation, the bifunctional catalysts are typically comprised of weakly acidic and basic catalyst units (e.g., **C6**, **C11**), and/or the reactions are performed using a large excess of solvent. Consequently, such

[6] (a) Page, M. I.; Jencks, W. P. *Proc. Natl Acad. Sci.* **1971**, *68*, 1678–1683. (b) Menger, F. M. *Acc. Chem. Res.* **1993**, *26*, 206–212. (c) Bruice, T. C.; Lightstone, F. C. *Acc. Chem. Res.* **1999**, *32*, 127–136. (d) Kennan, A. J.; Whitlock, H. W. *J. Am. Chem. Soc.* **1996**, *118*, 3027–3028.

processes demand highly acid- and/or base-sensitive pronucleophiles and electrophiles (e.g., 1,3-dicarbonyl compounds and *N*-Boc-substituted benzaldimines, respectively) that undergo racemic background reaction, and suffer from low reaction efficiency.

Efficient and enantioselective transformations can also be promoted using Lewis acidic and Lewis basic catalysts that are untethered and independently operational (e.g., **C1** and **C2**; Scheme 1.1).[3] The processes involving this class of catalysts allow for rapid catalyst optimization as this can be readily achieved without carrying out the cumbersome tethering processes (*vs* bifunctional catalysis).[1-2] Either one or both of the catalysts can be chiral; through the identification of a matching catalyst combination, both the reaction efficiency as well as enantio- and diastereo-selectivies can be improved. A representative method utilizes a combination of [SegPhos–Cu] complex **C1** and Barton's base **C2** (Scheme 1.3) which was developed by Shibasaki and co-workers that promote highly enantioselective Mannich-type reactions between 7-azaindolinylamide **1.4** and *N*-Boc-substituted benzaldemine **1.5** to afford **1.6** (Scheme 1.3).[3d] Despite such notable advances, highly efficient and enantioselective methods using the untethered cooperative catalysts remain underdeveloped.[1-2] This is mainly because the untethered acidic and basic catalysts can more readily undergo undesired mutual quenching (vs. bifunctional catalysts);[1-2] moreover, the catalysts can also be deactivated by forming stable complexes with the substrates, intermediates and products. One strategy to avoid the mutual quenching problem has been to utilize the catalyst combinations that have minimal electronic and steric affinities to interact with each other (e.g., soft Lewis acid **C1** and hard Brønsted base **C2**, both of them are sterically hindered; Scheme 1.3). However, when using mildly acidic catalysts such as the [SegPhos–Cu] complex **C1** or various H-bond donors (e.g., **C12**, Scheme 1.2), electrophiles that can be sufficiently activated

Scheme 1.3. Enantioselective Mannich-Type Reaction Promoted by a Chiral Cu-based Catalyst and a Brønsted Base Catalyst



are often confined to those that are highly acid-sensitive (e.g., *N*-Boc-substituted benzaldemine **1.5**). When more Lewis acidic catalysts that can activate less electrophilic substrates are employed; mutual quenching becomes problematic. Furthermore, the processes involving untethered catalysts do not benefit from the proximity effect observed in those using bifunctional catalysts, therefore resulting in relatively lower reaction efficiency.

Despite the limitations as described above, there has been key advances made in the development of enantioselective methods that rely of the cooperative actions of various untethered, independently operational catalysts. As shown in the examples above (Schemes 1.2 and 1.3), the cooperative acid/base catalysis has been widely applied in the context of enantioselective α-functionalization of carbonyl compounds; these methods often proceed through in situ generation of enolate equivalent intermediates by Brønsted base-catalyzed deprotonation of Lewis acid-activated carbonyl pronucleophiles.[1-2] To highlight both the significance and remaining unresolved problems of the state-of-the-art, a review on recent advances in enantioselective cooperative catalysis, with the focus on elucidating the limitations of enolate-related chemistry,

that served as intellectual foundations of this dissertation research is provided herein. This chapter covers topics as listed below. In Chapter 1.1, two selected recent examples of enantioselective processes promoted by the cooperative actions of two Lewis acid catalysts are highlighted. Then, a review on stereoselective transformations enabled by the use of three catalyst units are provided in Chapter 1.2.

Chapter 1.1: Enantioselective Transformations Promoted by Cooperative Functions of Two Lewis Acids

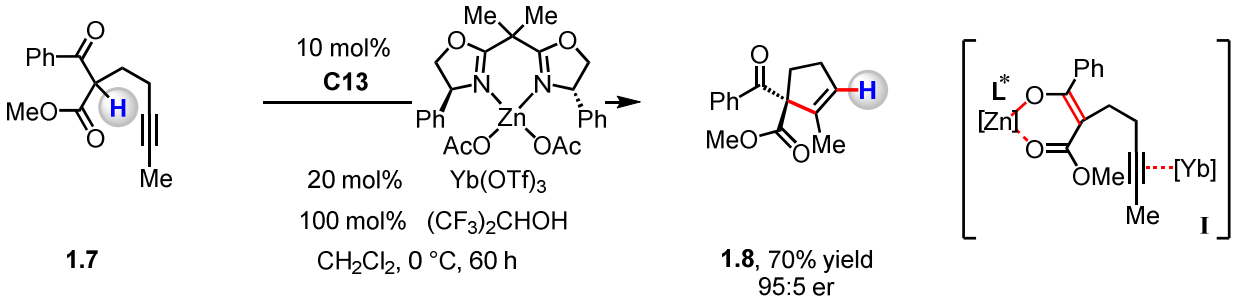
Chapter 1.2: Enantioselective Transformations Promoted by Cooperative Functions of Three Catalyst Units

Chapter 1.3: Aims of the Dissertation Research

1.1. Enantioselective Transformations Promoted by Cooperative Functions of Two Lewis Acids

Enantioselective cooperative acid/acid catalysis involves the use of two independent Lewis acids that work in concert to promote a desirable enantioselective transformation. A representative example includes the work by Shibata and co-workers, which revealed that a cooperative catalyst system consisting of a Zinc-PhBox complex **C13** and $Yb(OTf)_3$ promote enantioselective 5-*endo-dig* cyclization of 1,3-dicarbonyl compound **1.7** bearing an internal alkyne moiety (Scheme 1.4).[7] With **C13** as the only catalyst, the cyclized product **1.8** cannot be generated. When the Lewis acid cocatalyst $Yb(OTf)_3$ is incorperated, 5-*endo-dig* cyclization can proceed to produce **1.8** in 70% yield with 95:5 er. The author proposed that the Lewis acidic **C13** could activate dicarbonyl moiety of **1.7** to generate a nucleophilic zinc–enolate intermedaite while the soft Lewis acid $Yb(OTf)_3$ activates the electron-rich alkyne moiety (**I**). The subsequent enantioselective Conia-ene-type cyclization between the enolate and electrophilic $Yb(OTf)_3$/alkyne complex would deliver **1.8**. However, this transformation only occurs with readily enolizable dicarbonyl compounds; less

Scheme 1.4. Catalytic Enantioselective 5-*endo-dig* Carbocyclization of *β*-Ketoesters through Cooperative Functions of Chiral Zinc-based Lewis Acid and $Yb(OTf)_3$

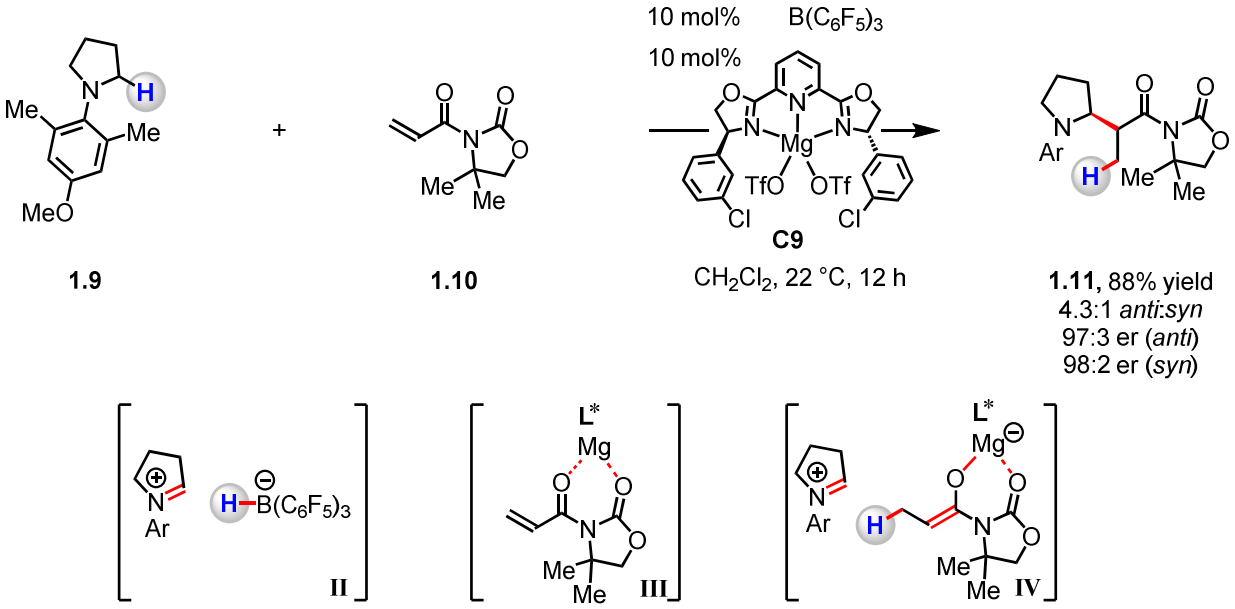


[7] Suzuki, S.; Tokunaga, E.; Reddy, D. S.; Matsumoto, T.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 4131–4135.

base-sensitive mono-carbonyl pronucleophiles (ketones, ester, amides and thioesters) are not shown to be compatible. This is mainly because the catalyst system comprised of Zn- and Yb-based complexes is not compatible with Brønsted basic catalysts (e.g., DBU, Barton's base) that may be capable of deprotonating the desirable mono-carbonyl substrates.

Another representative method utilizes a combination of an achiral organoborane and a chiral Mg–PyBOX complex **C9** that promotes enantioselective α-amino C–H alkylation of *N*-alkylamine **1.9** (Scheme 1.5).[3g] When only $B(C_6F_5)_3$ was present in the reaction mixture, the desired product **1.11** was obtained in < 5% yield. However, by introducing the chiral Lewis acid co-catalyst **C9**, **1.11** can be generated in up to 88% yield and 98:2 er. The plausible mechanism involves abstraction of a hydride from an α-amino C–H unit of *N*-alkylamine **1.9** by $B(C_6F_5)_3$ to generate a borohydride and an iminium ion (**II**); at the same time, the Lewis acidic Mg–PyBOX complex **C9** activates an α,β-unsaturated substrate **1.10** (**III**); ensuing borohydride reduction of PyBOX–Mg-activated **1.10** furnishes a chiral Mg–enolate intermediate (**IV**). Then, diastereo- and enantioselective C–C bond forming reaction between the iminium ion and the enolate affords the α-alkylation product **1.11**.

Scheme 1.5. Direct Enantioselective α-C–H Functionalization of Amines through Cooperative Action of Chiral and Achiral Lewis Acid Catalysts



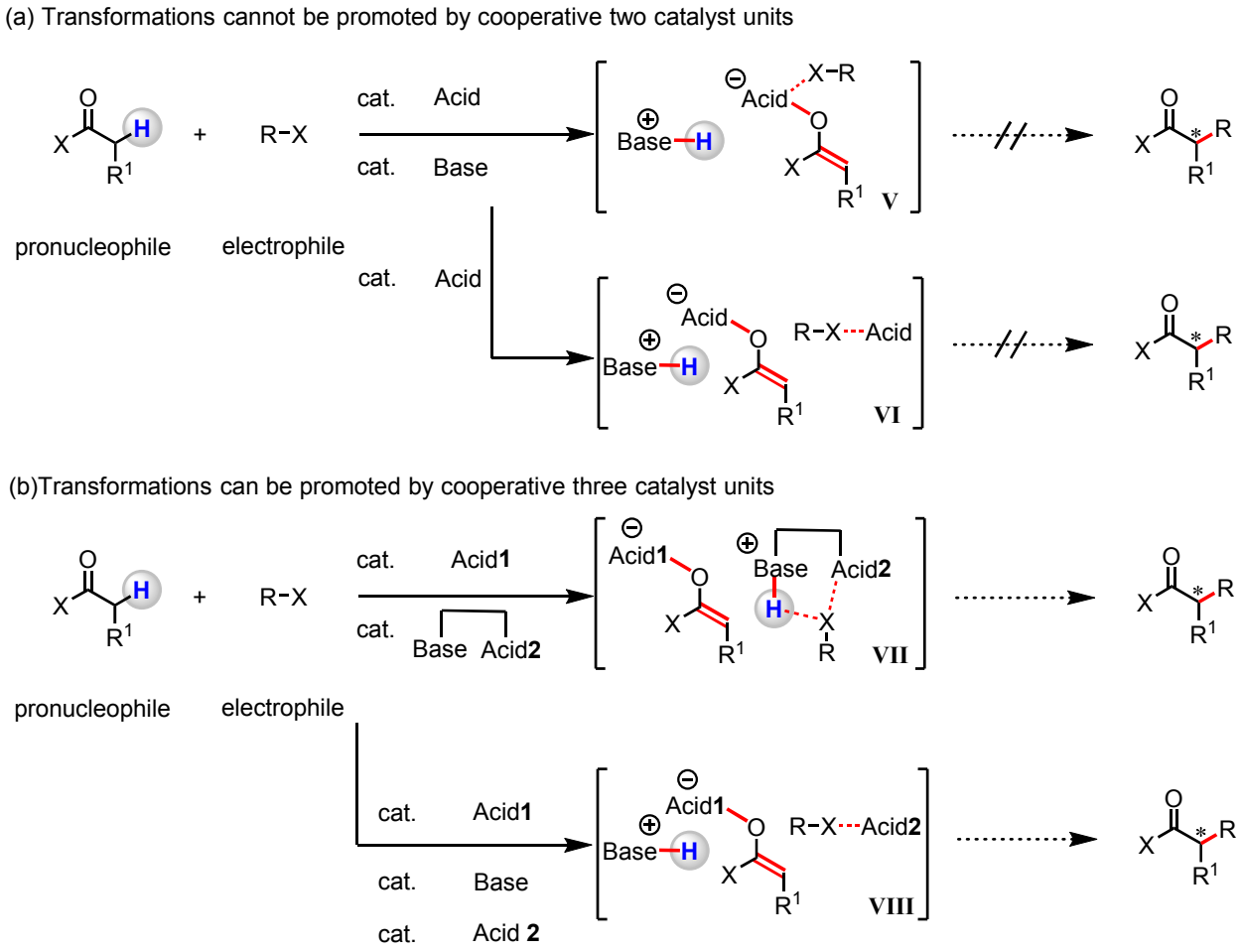
1.2. Enantioselective Transformations Promoted by Cooperative Functions of Three Catalyst Units

This section highlights the state-of-the-art of enantioselective α-functionalization of carbonyl compounds promoted by cooperative functions of three catalyst units.[8] Carbonyl α-functionalization is often achieved through in situ generation of enolate equivalents by activation of the pronucleophile's carbonyl unit by an acidic catalyst, followed by deprotonation of α-carbonyl C–H bond by a Brønsted Base (**pronucleophile** $\rightarrow$ **V**, Scheme 1.6a). The subsequent reaction between the enolate and an appropriate electrophile can be promoted by the enolate-bound Lewis acid (**V**). Alternatively, another equivalent of the Lewis acid may activate the electrophile (**VI**). Nonetheless, there can be instances when a target reaction cannot proceed because the electrophile cannot be sufficiently activated by the Lewis acid used for the activation of the carbonyl-based pronucleophiles. Such complication may be remedied through the employment of a catalyst system comprised of a Lewis acid catalyst used in pair with a bifunctional catalyst, latter of which is comprised of a Brønsted base and an acidic catalyst unit (Scheme 1.6b). Alternatively, a catalyst system which constitutes of two acidic catalysts and a Brønsted base catalyst that are untethered and independently operational can be employed (Scheme 1.6b). Using these three-catalyst unit systems, carbonyl-based pronucleophiles may be readily converted into the corresponding enolate equivalents by the cooperative actions of their Lewis acidic and Brønsted

[8] For selected reports on enantioselective transformations promoted by ternary catalysts, see: (a)Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc*. **2010**, *132*, 5522–5531. (b) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc*. **2010**, *132*, 10275–10277. (c) Iwata, M.; Yazaki, R.; Chen, I. H.; Sureshkumar, D.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc*. **2011**, *133*, 5554–5560. (d) Jiang, G.; List, B. *Angew. Chem*., *Int. Ed*. **2011**, *50*, 9471–9474. (e) Capacci, A. G.; Malinowski, J. T.; McAlpine, N. J.; Kuhne, J.; MacMillan, D. W. C. *Nat. Chem*. **2017**, *9*, 1073–1077. (f) Jiang, X.; Boehm, P.; Hartwig, J. F. *J. Am. Chem. Soc*. **2018**, *140*, 1239–1242. (g) Hayashi, Y.; Umekubo, N. *Angew. Chem*., *Int. Ed*. **2018**, *57*, 1958–1962. (h) Chen, L.; Luo, M. J.; Zhu, F.; Wen, W.; Guo, Q. X. *J. Am. Chem. Soc*. **2019**, *141*, 5159–5163. (i) Cao, M.; Yesilcimen, A.; Wasa, M. *J. Am. Chem. Soc*. **2019**, *141*, 4199–4203. (j) Chang, Y.; Cao, M.; Chan, J. Z.; Zhao, C.; Wang, Y.; Yang, R.; Wasa, M. *J. Am. Chem. Soc*. **2021**, *143*, 2441–2455.

basic catalysts, while the other acidic catalyst can be dedicated for the activation of electrophiles (through intermediates **VII** or **VIII**, Scheme 1.6b). Through this approach, α-functionalization reactions involving a significantly broader range of pronucleophiles and electrophiles may be achieved.

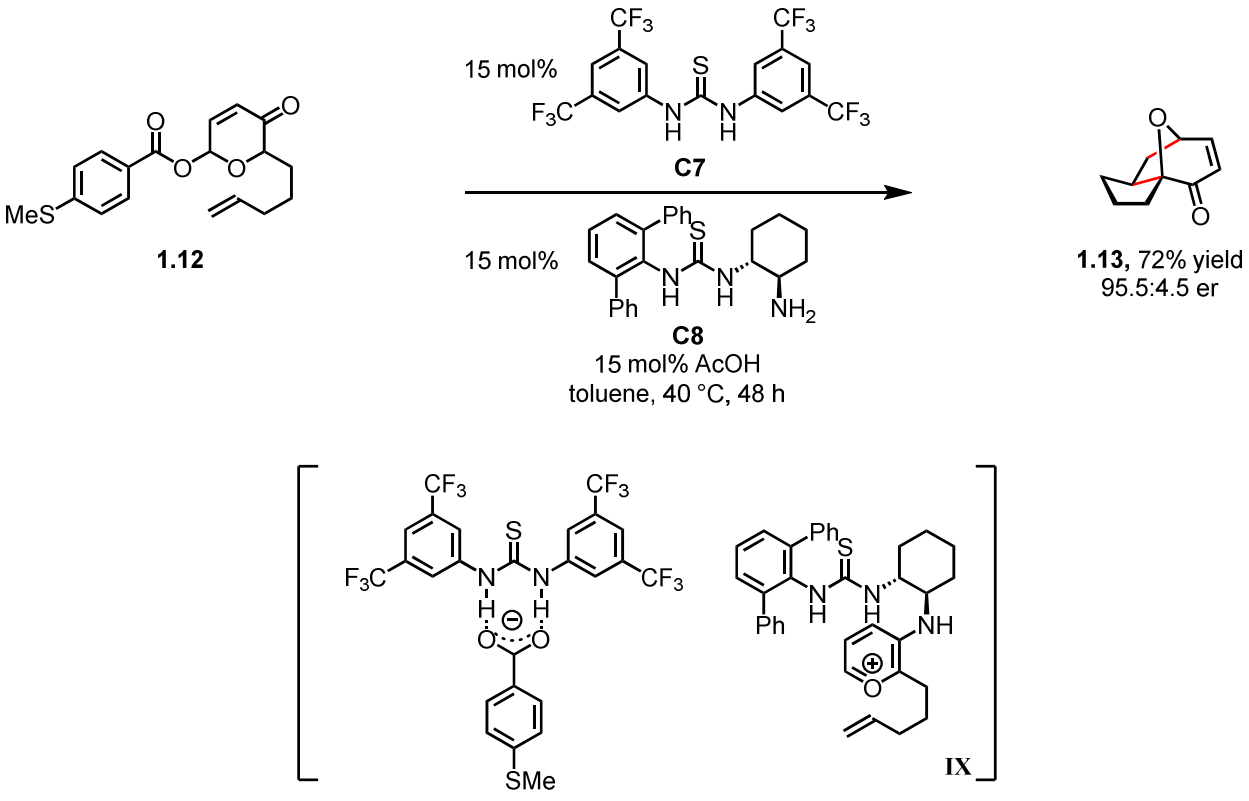
Scheme 1.6. α-Functionalization of Carbonyl Compounds Promoted by Cooperative Catalysts



One representative example is the enantioselective intramolecular [5+2] cycloaddition reaction of racemic pyranone **1.12** to provide chiral 8-oxabicyclo[3.2.1]octane derivatives **1.13** promoted by cooperative actions of an achiral thiourea **C7** and a bifunctional catalyst **C8** consisting of a dual H-bond donor and a Lewis basic primary amine unit (Scheme 1.7).[3b] When only bifunctional catalyst **C8** was present in the reaction mixture, the cycloaddition product **1.13**

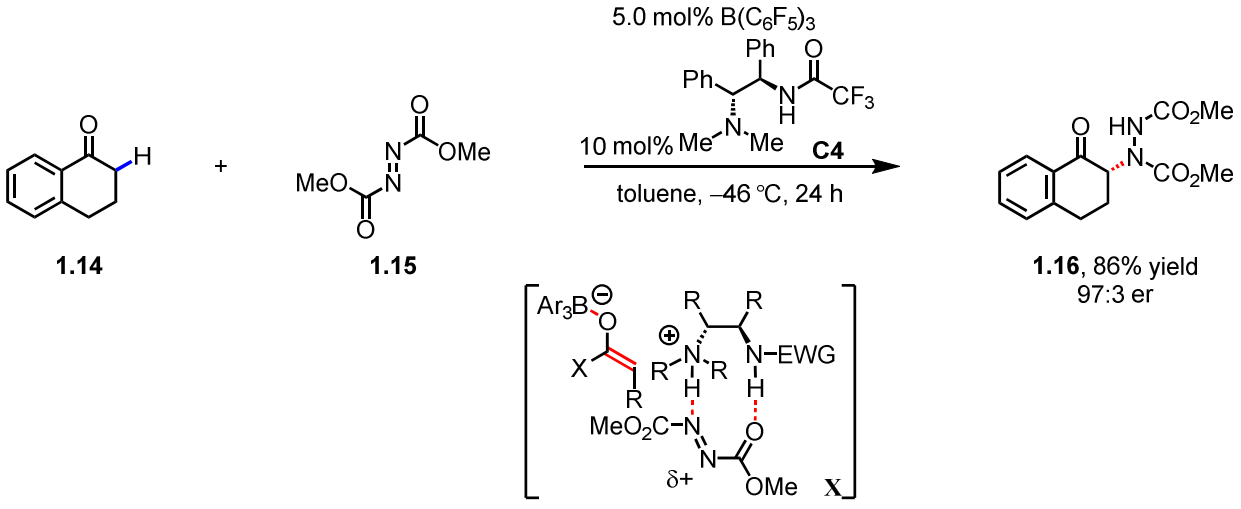
was obtained in only 32% yield with 86:14 er. However, by introducing achiral **C7**, both the yield and er could be improved to 72% and 95.5:4.5, respectively. The proposed modes of substrate activation involve efficient cleavage of C–OC(=O)Ar bond contained in **1.12** by more acidic **C7** (relative to less acidic **C8**), and a primary amine unit of **C8** undergoes condensation with a carbonyl group of **1.12**, thereby leading to the formation of pyrylium intermediate **IX**. Ensuing enantioselective [5+2] cycloaddition results in the formation of desired product **1.13**. However, this reaction demands high catalyst loading, longer reaction time, as well as substrates that possess highly acid-sensitive leaving group; these issues likely arise because of the use of weakly acidic H-bond donor catalysts.

Scheme 1.7. A Bifunctional Catalyst and an Achiral Thiourea Promoted Enantioselective Intramolecular [5 + 2] Cycloadditions



Recently, our group developed enantioselective α-amination of mono-carbonyl compounds catalyzed by a Lewis acidic $B(C_6F_5)_3$ and a bifunctional catalyst **C4**, which contains a Brønsted basic trialkylamine moiety and a hydrogen bond donor (Scheme 1.8).[3e] When $B(C_6F_5)_3$ and Hünig's base (which lacks the tethered H-bond donor as seen in **C4**) were used, ***rac*-1.16** was produced at a substantially slower rate. However, with $B(C_6F_5)_3$ and **C4**, the reaction proceeds more efficiently to generate the enantioenriched α-amino carbonyl compound in 86% yield with 97:3 er. These results suggest that $B(C_6F_5)_3$ activates the carbonyl moiety of **1.14**, and the trialkylamine unit of **C4** deprotonates it to afford an intermediate comprised of a boron–enolate and **C4**-derived ammonium ion (**1.14** → **X**). The ammonium ion and the amide units serve as dual H-bond donors to activate **1.15**, while positioning it in close proximity to the in-situ generated boron–enolate, which is ionically bound to the ammonium ion (**X**). Thus, highly efficient and enantioselective α-amination between **1.14** and **1.15** can be achieved to provide **1.16**. Despite this advance, a key unresolved problem remained to be addressed: the use of weakly acidic dual H-

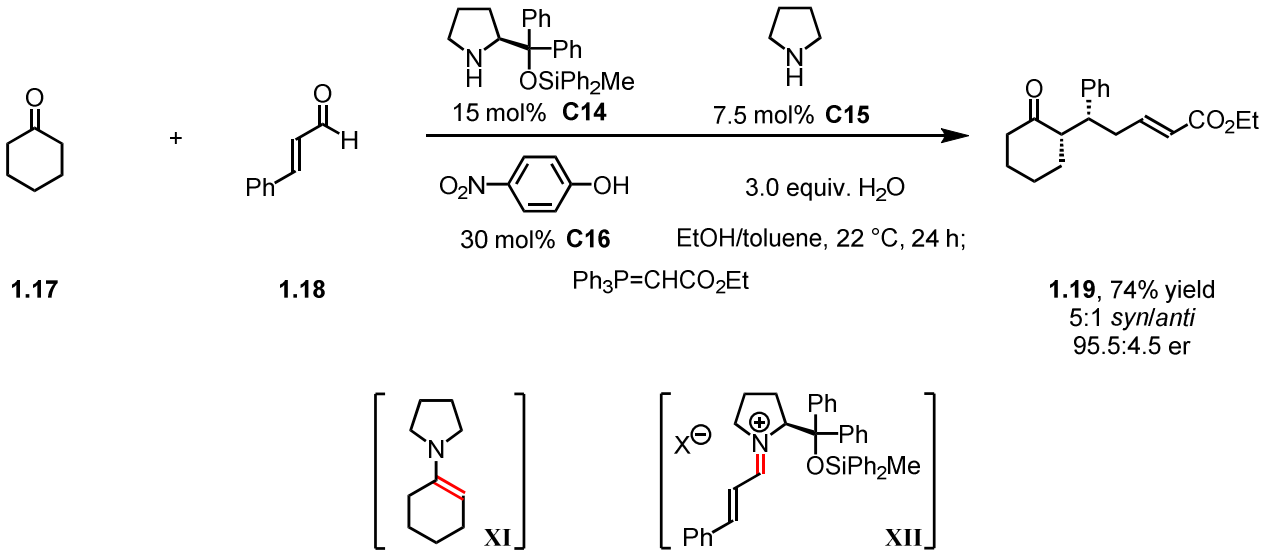
Scheme 1.8. Direct Catalytic Enantioselective α-Amination of Carbonyl Compounds Promoted by $B(C_6F_5)_3$ and a Bifunctional Catalyst



bond donors did not allow less pre-activated electrophiles (e.g., *N*-alkylimine, ketones) to react with **1.14**. Such limitation leads us to investigate the catalyst systems that incorporate strongly Lewis acidic co-catalysts that are to be described in the latter chapters of this dissertation.

Hayashi and co-workers developed an enantioselective Michael reaction of ketone **1.17** and α,β-unsaturated aldehyde **1.18** using a cooperative catalyst system consisting of diphenylprolinol trimethylsilyl ether **C14**, pyrrolidine **C15**, and Brønsted acidic phenol derivative **C16** (Scheme 1.9).[8g] With **C15** and **C16** as the only catalysts, *rac*- **1.19** was obtained. However, by incorporating **C14** as the co-catalyst, the reaction can proceed more efficiently and produce **1.19** in 74% yield, 5:1 dr and 94.5:4.5 er. The authors proposed that ketone **1.17** can be selectively activated by **C15** and **C16** to generate nucleophilic enamine intermediate **XI**, while α,β-unsaturated aldehyde **1.18** would be activated by **C14** and **C16** to deliver the more electrophilic iminium ion intermediate **XII** (vs the iminium ion generated from **1.18** and **C15**). The subsequent enantioselective C–C bond formation between the nucleophilic enamine **XI** and electrophilic

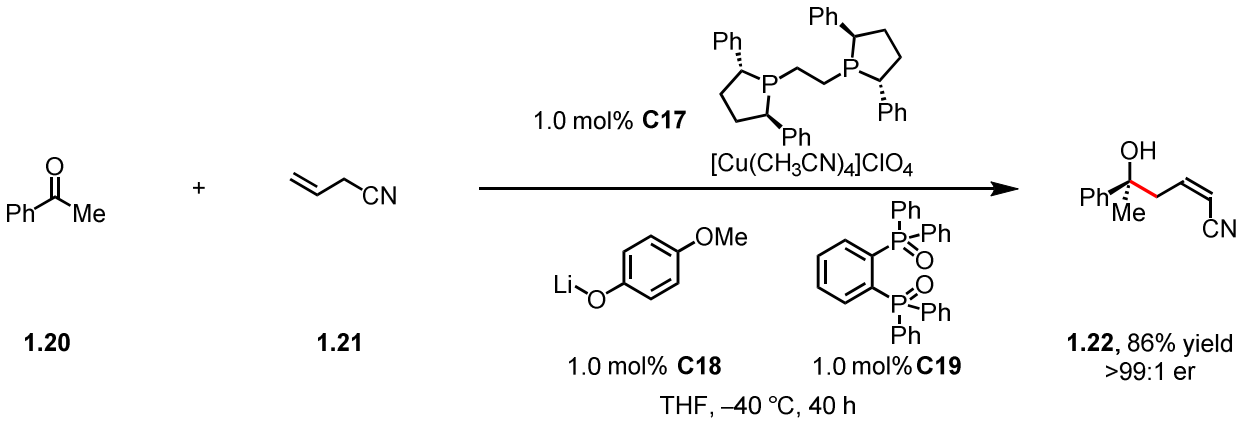
Scheme 1.9. Direct Enantioselective Michael Reaction Catalyzed by a Combination of Two Secondary Amine Catalysts and a Brønsted Acid Catalyst

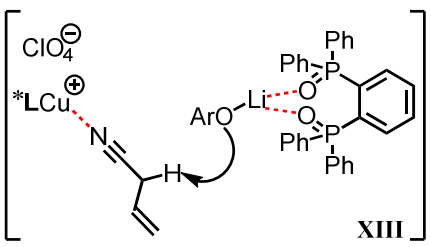


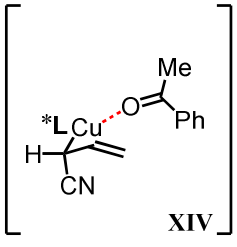
iminium ion **XII** followed by Wittig reaction would produce **1.19**. Despite the important advances described, this method is confined to less hindered and sufficiently electrophilic ketones and aldehydes that readily undergo condensation with the secondary amine catalysts.

In 2011, Shibasaki and co-workers utilized a combination of Cu/(*R*,*R*)-Ph-BPE **C17**, LiOAr **C18** and a phosphine oxide **C19** to promote enantioselective γ-addition of but-3-enenitrile **1.21** to acetophenone **1.20** producing enantioenriched homoallylic alcohol **1.22** (Scheme 1.10).[8a] While homoallylic alcohol **1.22** can be generated in 83% yield with 97.5:2.5 er using 10 mol% **C17** and **C18** as the only catalysts, by incorporating of Lewis base **C19,** the catalyst loading significantly lowers to 1.0 mol% (86% yield with >99:1 er). Kinetic studies revealed that deprotonation of Lewis acid L_n–Cu-activated **1.21** by **C18** was the rate-determining step (**XIII**).

Scheme 1.10. Enantioselective Addition of Allyl Cyanide to Ketones Promoted by Soft Lewis Acid/Hard Brønsted base/Hard Brønsted Base Catalysts



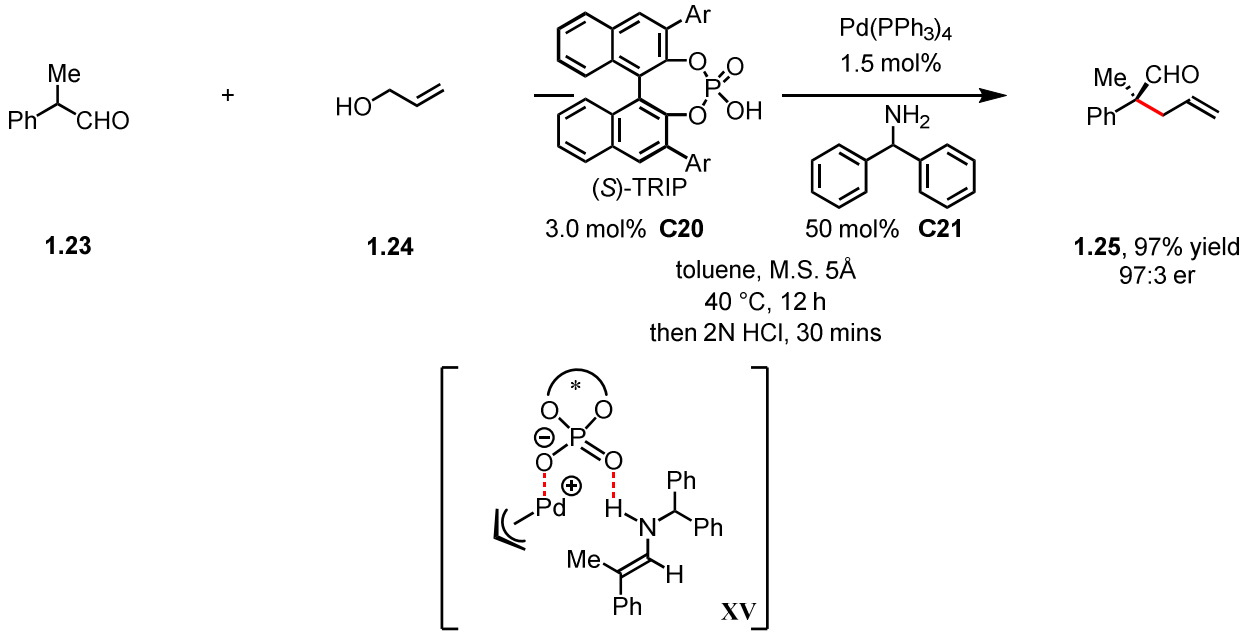




Thus, **C19** enhancing the basicity of **C18** through coordination to the Li cation. Then, the ensuing enantioselective γ-addition of the in situ generated Cu–nucleophile to the Cu-activated ketone **1.20** delivers the enantioenriched homoallylic alcohol **1.22** (**XIV**).

List and co-workers developed enantioselective α-allylation of aldehyde **1.23** utilizing a cooperative catalyst system consisting of a chiral phosphoric acid (*S*)-TRIP **C20**, $Pd(PPh_3)_4$ and *N*-benzhydryl amine **C21** (Scheme 1.11).[8d] When only **C20** and $Pd(PPh_3)_4$ were employed, allylation product **1.25** was obtained in 55:45 er. In contrast, incorporation of *N*-benzhydryl amine **C21** significantly improved the enantioselectivity to 97:3 er. The proposed modes of substrate activation involve generation of an enamine intermediate through the reaction of primary amine catalyst **C21** and aldehyde **1.23**; at the same time, $Pd(PPh_3)_4$ reacts with allyl alcohol **1.24** to form an π-allyl complex **XV**. Phosphoric acid **C20** catalyzes the generation of a Pd/allyl complex while bringing the nucleophilic enamine intermediate and electrophilic π-allyl complex in close

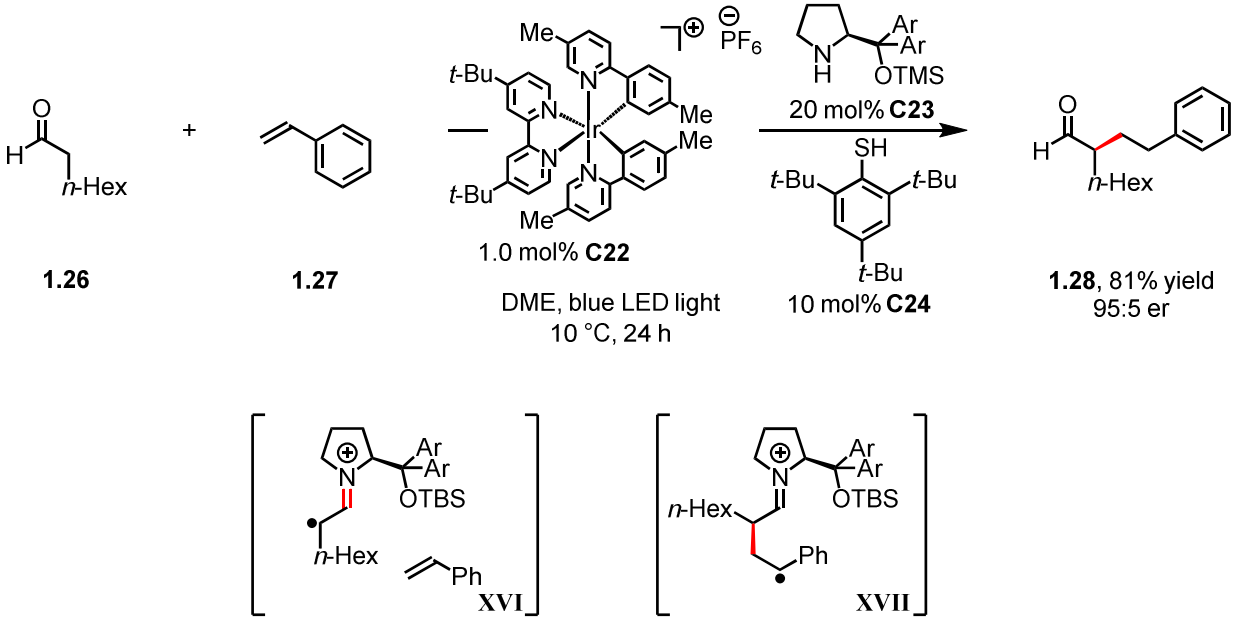
Scheme 1.11. Enantioselective α-Allylation of Aldehyde by the Concerted Action of Three Different Catalysts



proximity (**XV**) to facilitate the enantioselective allylation, thereby producing **1.25**. However, the scope of pronucleophiles is limited to aldehydes that can readily undergo condensation with **C21**.

MacMillan and co-workers developed enantioselective α-alkylation of aldehyde **1.26** with styrene **1.27** by using a catalyst combination of an Ir(III)-based photocatalyst **C22**, a chiral amine catalyst **C23**, and a thiol, which serves as a hydrogen atom transfer (HAT) catalyst **C24** (Scheme 1.12).[8e] With only **C22** and **C23**, the α-alkylated product **1.28** was obtained in <10 % yield. By incorporating a HAT catalyst **C24**, **1.28** could be obtained in 81 % yield with >95:5 er. The authors proposed that the process begins with condensation of amine catalyst **C23** and **1.26** to provide an enamine intermediate, which is then oxidized by **C22** to produce an enaminyl radical intermediate **XVI** by single electron transfer. Then, the electrophilic radical **XVI** would undergo stereoselective addition to styrene **1.27** to generate a new C–C bond with a secondary alkyl radical (**XVI** → **XVII**).

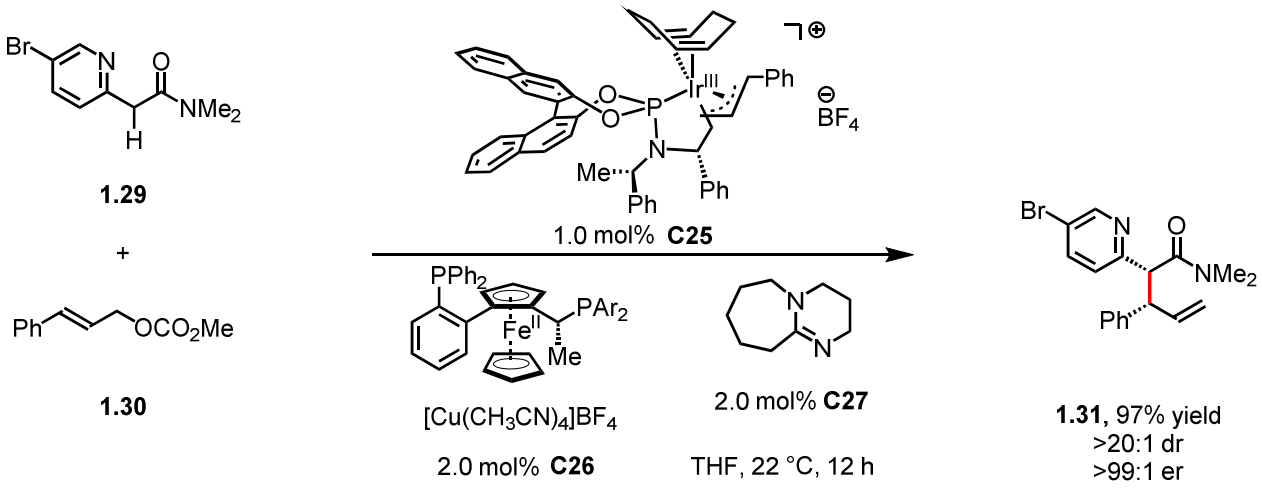
Scheme 1.12. Enantioselective α-Alkylation of Aldehyde Using Simple Olefins Promoted by Ir(III) Photoredox/Secondary Amine/Thiol catalysts

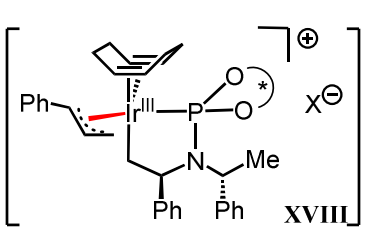


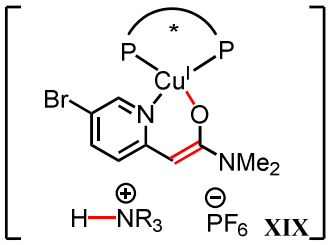
Then, hydrogen atom transfer between nucleophilic radical **XVII** and **C24** would deliver the desired product **1.28**. However, this transformation demands the use of precious Ir-based catalyst and the substrate scope is limited to styrene derivatives, thus severely limiting the applicability of this method.

Hartwig and co-workers disclosed a stereodivergent allylation of azaaryl acetamide **1.29** and acetate **1.30** by synergistic functions of an Ir-based catalyst **C25**, a copper-based catalyst **C26**, and DBU **C27** (Scheme 1.13).[8f] While allylation product **1.31** could be produced in only 14 % yield with 1:1.8 dr using **C25** and DBU as the only catalysts, incorporation of Lewis acid **C26** significantly improves both the reaction yield and stereoselectivity (97% yield, >20:1 dr and >99:1 er). The postulated mechanism is that **C25** generates an electrophilic π-allyl complex from **1.30** (**XVIII**) while Lewis acidic Cu-based catalyst **C26** binds to **1.29** and lowers its pK_a so that it can be deprotonated by DBU (**XIX**). The ensuing stereoselective allylation between the in-situ generated nucleophilic Cu(I) enolate (**XIX**) and electrophilic π-allyl complex (**XVIII**) would produce allylation product **1.31**. Furthermore, the authors demonstrated that by using different combinations of catalyst enantiomers, stereodivergent allylation can be achieved to produce all four stereoisomers of **1.31** with excellent diastereoselectivity and enantioselectivity. However, the requirement for the use of biscoordination azaaryl acetamide derivatives as the substrates as well as the precious Ir-based catalyst are the practical limitations of this method.

Scheme 1.13. Stereodivergent Allylation Promoted by Cooperative Functions of an Ir-based Catalyst, a Cu-based Catalyst, and DBU







1.3. Aims of the Dissertation Research

Despite the advances in the enantioselective transformations that exploit the synergistic functions of two and/or more catalyst units as highlighted above, fundamental problems remain to be addressed:

Key problem 1. Catalyst/substrate combination is strictly restricted to those that can circumvent undesirable acid–base complexation; Lewis acid- and/or Lewis base-sensitive functional groups are poorly tolerated.

Key problem 2. Weakly to moderately acidic and basic catalysts are often employed. Thus, transformations that rely on cooperative catalysis demand the use of highly base sensitive pronucleophiles (e.g., 1,3-dicarbonyl compounds, nitroalkanes, cyanoalkanes, aldehyde) and acid sensitive electrophiles (e.g., *N*-Boc-substituted benzaldimines, nitroalkenes).

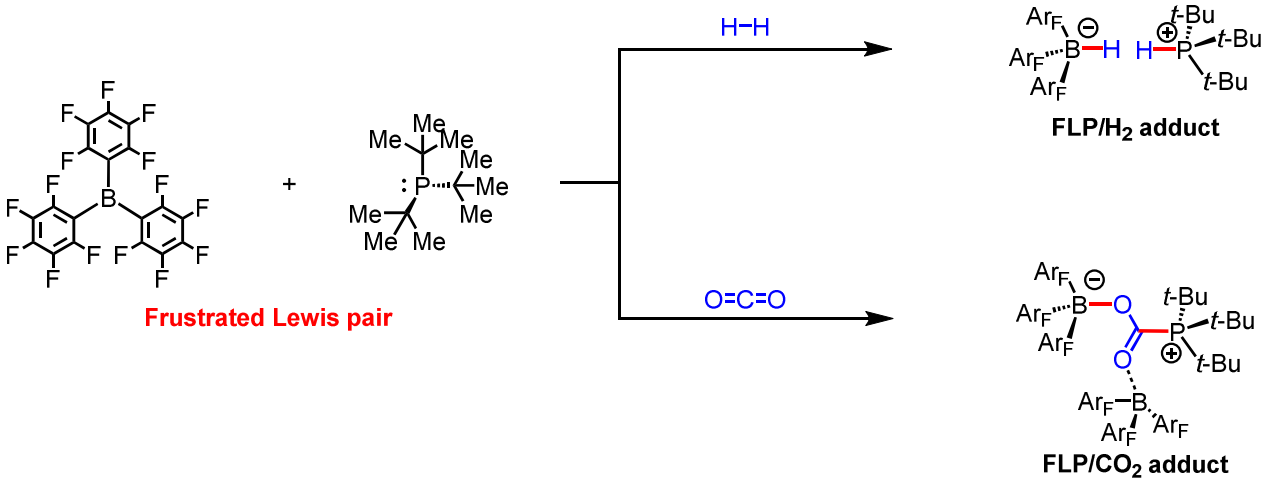
Key problem 3. Reaction efficiency is typically poor, thereby requires the use of higher catalyst loading and longer reaction time.

In an effort to overcome the key limitations as listed above, we envisioned the application of "frustrated" Lewis pair complexes (i.e., FLP) as enantioselective cooperative catalysts.[9] The FLPs typically are comprised of a strongly Lewis acidic organoborane and an appropriate Lewis base such as a tertiary amine or an organophosphine. These sterically encumbered and electronically disparate acids and bases are able to circumvent the undesirable acid–base complexation. These FLPs have been shown to activate an array of otherwise unreactive small

[9] (a) Welch, G. C.; San Juan, R. R.; Masuda, J. D.; Stephan, D. W. et al. *Science* **2006**, *314*, 1124–1126. (b) Momming, C. M.; Otten, E.; Kehr, G.; Frolich, R.; Grimme, S.; Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 6643–6646. (c) Dobrovetsky, R.; Stephan, D. W. *J. Am. Chem. Soc.* **2013**, *135*, 4974–4977. (d) Grimme, S.; Stephan, D. W.; Erker, G. *Chem. Sci.* **2013**, *4*, 213–219. (e) Grimme, S.; Erker, G. *J. Am. Chem. Soc.* **2016**, *138*, 4302–4305.

molecules such as H_2, CO_2, CO, SO_2 to form the corresponding adducts (Scheme 1.14); notably, these small molecules cannot be activated using the preexisting cooperative catalysts that are comprised of weaker Lewis acids and/or H-bond donors (e.g., **C1/C2**, **C5/C6**, and **C7/C8**, Scheme 1.1). Nonetheless, the development of FLP-catalyzed transformations had been confined to hydrogenation of unsaturated compounds at the time this dissertation research was started in 2016.

Scheme 1.14. Stoichiometric Activation of H_2 and CO_2 by FLP

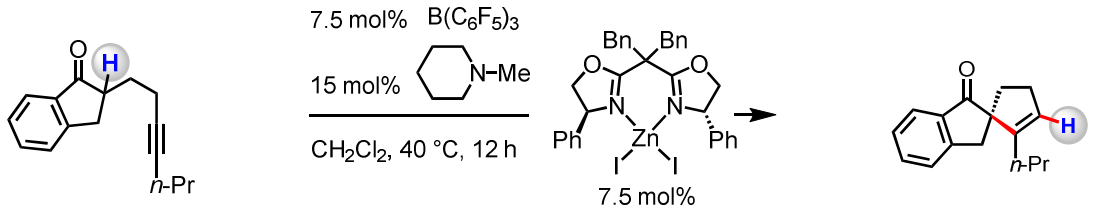


We envisioned that a catalyst system comprised of $B(C_6F_5)_3$, a chiral Lewis acid co-catalyst and a N-based Brønsted base can promote enantioselective C–C and C–heteroatom bond forming reactions between a broad array of pronucleophiles and electrophiles. We thought that the **key problems 1** and **2** mentioned above can be remedied through the use of the FLP catalysts as they are largely immune to acid–base complexation. Moreover, the substrate scope could be broadened because the FLP catalysts may not form stable adducts with Lewis acid- and/or base-sensitive functional groups. Thus, our FLP-catalyzed transformations may be applicable to synthesis as well as late-stage functionalization of structurally complex pharmaceuticals and precursors for natural products. The **key problem 3** related to poor reaction efficiency and high catalyst loading could

also be addressed through the use of FLP catalysts; less permanent catalyst–substrate, catalyst–intermediate, and catalyst–product interactions may translate into higher reaction efficiency, and therefore lower catalyst loading may be achieved. The enantioselective transformations to be described in this dissertation include FLP-catalyzed Conia-ene-type reaction involving alkynyl carbonyl compounds (Scheme 1.15a, see Chapter 2), and FLP-catalyzed alkylation of β-amino C–H bonds (Scheme 1.15b, see Chapter 3). Through the development of these methods, we aim to demonstrate the proof of concept that the FLP catalysts are capable of overcoming the aforementioned fundamental limitations of enantioselective cooperative catalysis; specifically, poorly acid- and/or base-sensitive substrates that possess an array of different functional groups undergo efficient and highly enantioselective C–C bond forming reactions while overcoming the undesirable catalyst deactivation due to mutual quenching.

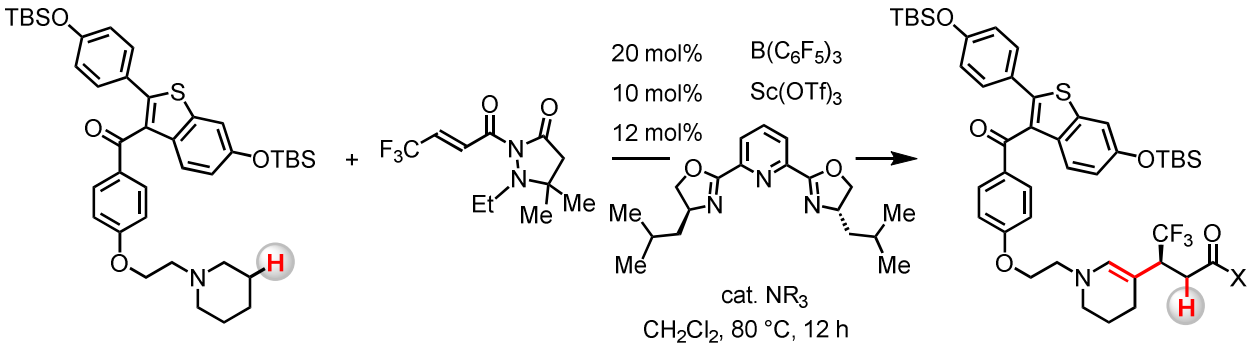
Scheme 1.15. Enantioselective Transformations to be Described in this Dissertation

(a) Enantioselective Conia-Ene-Type Reaction



98% yield
99:1 er

(b) Enantioselective β-Amino C–H Functionalization



raloxifene derivative

57% yield
95:5 er

Chapter Two

Enantioselective Conia-Ene-Type Cyclizations of Alkynyl Ketones through Cooperative Action of $B(C_6F_5)_3$, -Alkylamine and a Zn-Based Catalyst

Introduction

Enantioselective α-functionalization of carbonyl compounds represents one of the most powerful and widely employed methods for the formations of C–C bonds or C–heteroatom bonds.[1] However, as described in Chapter 1, the processes that employ combinations of weakly acidic and basic catalysts demand highly acid- and/or base-sensitive pronucleophiles and electrophiles (e.g., 1,3-dicarbonyl compounds and nitroalkenes, respectively). Development of enantioselective α-functionalization reaction involving less base-sensitive mono-carbonyl compounds (e.g., ketones, esters, amides, thioesters; pK_a = 20-30) and poorly acid-sensitive electrophiles (e.g., electron-rich alkynes, CO_2, among others) stands as a formidable challenge.[2] In this chapter, we describe our studies that were aimed at facilitating the α-functionalizations of various mono-carbonyl compounds with different electrophiles through the use of FLP catalysts.

---

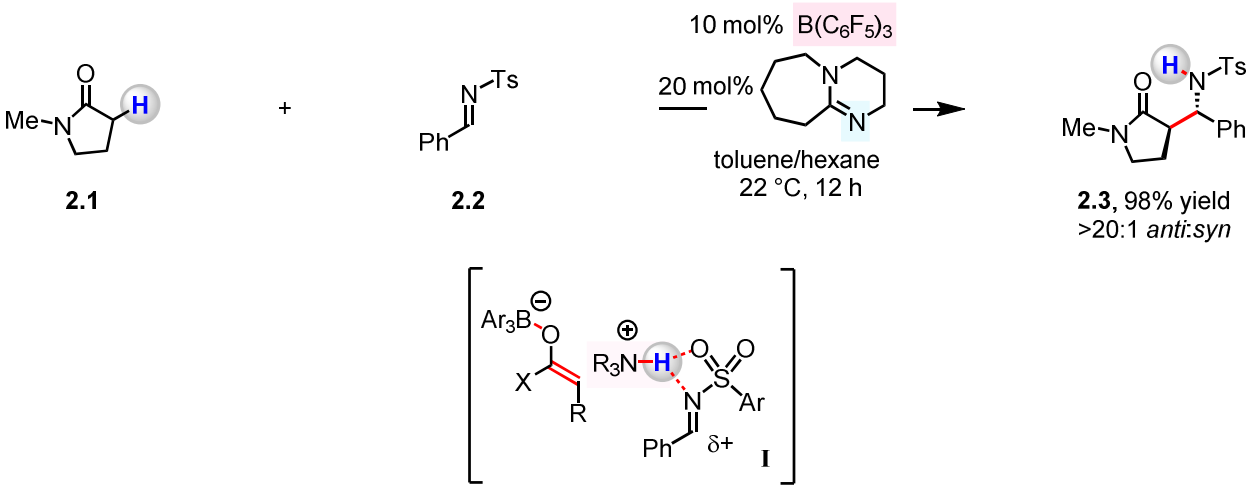
[1] For selected reviews, see: (a) Evans, D. A. in *Asymmetric Synthesis*, *Vol. 3* (Ed.: Morrison, J. D.), Academic Press, Orlando, 1984, 1−10. (b) Enders, D. in *Asymmetric Synthesis*, *Vol. 3*, *1st ed*. (Ed.: Morrison, J. D.), Academic Press, Orlando, 1984, 275−339. (c) Mekelburger, H. B.; Wilcox, C. S. in *Comprehensive Organic Synthesis*, *Vol. 2* (Eds.: Trost, B. M.; Fleming I.), Pergamon, Oxford, 1991, 99−131. (d) Heathcock C. H. in *Modern Synthetic Methods*, *Vol*. 6 (Ed.: Scheffold, R.), Helvetica Chimica Acta, Basel, 1992, 183−213. (e) Rizzacasa, M. A.; Perkins M. in *Stoichiometric Asymmetric Synthesis*, Sheffield Academic Press, Sheffield, 2000. (f) Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292-4300. (g) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *112*, 1082−1146. (h) Smith, A. M. R.; Hill, K. K. *Chem. Rev.* **2011**, *113*, 1637−1656. (i) Cano, R.; Zakarian, A.; McGlacken, G. P. *Angew. Chem., Int. Ed.* **2017**, *56*, 9278−9290.

[2] For selected reviews on enantioselective cooperative catalysis, see: (a) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924−1942. (b) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626−2704. (c) Allen, A. E.; MacMillan, D. W. *Chem. Sci*. **2012**, *3*, 633−658. (d) Trost, B. M.; Bartlett, M. J. *Acc. Chem. Res.* **2015**, *48*, 688−701. (e) Shibasaki, M.; Kumagai, N. in *Cooperative Catalysis: Designing Efficient Catalysts for Synthesis*, Peters, R., Eds.; Wiley-VCH: New York, 2015; Chapter 1. (f) Lu, X.; Deng, L. in *Cooperative Catalysis: Designing Efficient Catalysts for Synthesis*, Peters, R., Eds.; Wiley-VCH: New York, 2015; Chapter 5. (g) Inamdar, S. M.; Shinde, V. S.; Patil, N. T. *Org. Biomol. Chem.,* **2015**, *13*, 8116−8162. (h) Wang, M. H.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2016**, *55*, 14912−14922. (i) Romiti, F.; del Pozo, J.; Paioti, P. H. S.; Gonsales, S. A.; Li, X.; Hartrampf, F. W. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2019**, *141*, 17952−17961. (j) Sancheti, S. P.; Urvashi, Shah, M. P.; Patil, N. T. *ACS Catal.* **2020***, 10*, 3462-3489.

2.1. Frustrated Lewis Acid/Brønsted Base Catalysts for α-Functionalization of Carbonyl Compounds

In 2016, our group demonstrated that sterically hindered and electronically disparate $B(C_6F_5)_3$ and a N-based Brønsted base catalyst can promote direct catalytic Mannich-type reaction of ketone, ester or amide pro-nucleophiles (pK_a = 20-30) (Scheme 2.1).[3] $B(C_6F_5)_3$ is thought to activate the carbonyl compound **2.1** and lower its pK_a, thus allowing for DBU to deprotonate its acidic α-carbonyl C–H bond to generate an ion pair consisting of a boron–enolate and an ammonium ion (**I**). The latter component may then serve as a Brønsted acid to activate an imine substrate **2.2**, which would then react with the boron–enolate to afford a β-aminocarbonyl product **2.3**.

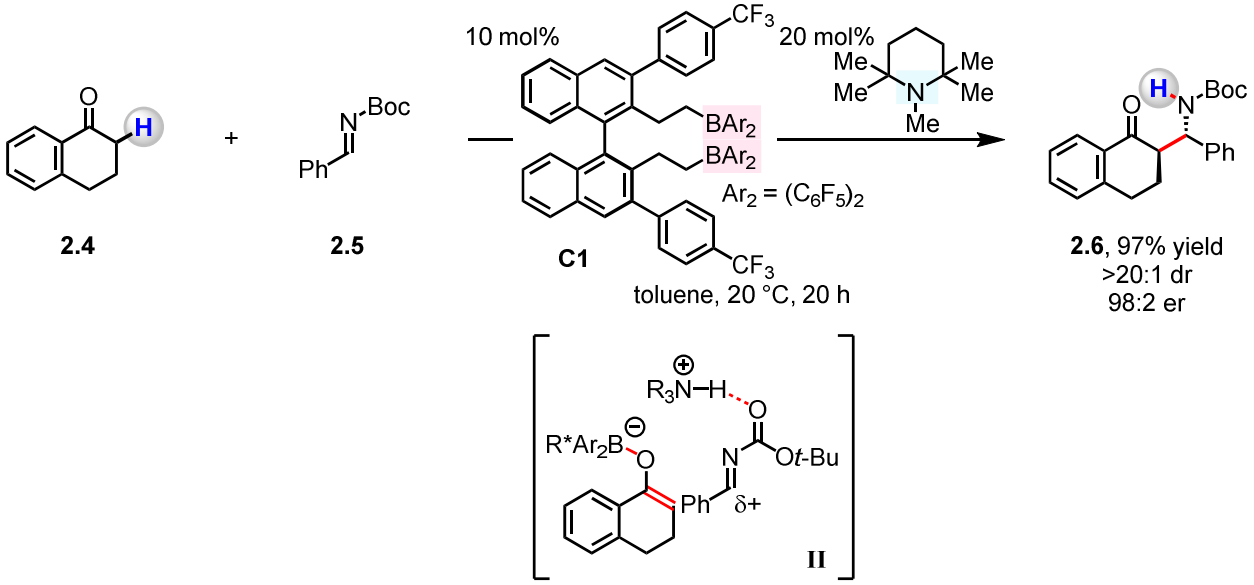
Scheme 2.1. Direct Mannich-Type Reaction Catalyzed by Frustrated Lewis Acid/Brønsted Base Complexes



[3] Chan, J. Z.; Yao, W.; Hastings, B. T.; Lok, C. K.; Wasa, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 13877–13881. (b) Shang, M.; Wang, X.; Koo, S. M.; Youn, J.; Chan, J. Z.; Yao, W.; Hastings, B. T.; Wasa, M. *J. Am. Chem. Soc.* **2017**, *139*, 95–98.

In a subsequent work, our group developed enantioselective Mannich-type reaction of mono-carbonyl compounds catalyzed by a chiral organoborane **C1** and pentamethylpiperidine (PMP, Scheme 2.2).[4] The cooperative functions of **C1** and PMP enables generation of a chiral boron–enolate from **2.4**, which then reacts with the ammonium ion-activated *N*-Boc-benzaldimine **2.5** (**II**) to afford an enantioenriched *β*-aminocarbonyl product **2.6**.

Scheme 2.2. Enantioselective Direct Mannich-Type Reaction Catalyzed by Frustrated Lewis Acid/Brønsted Base Complexes



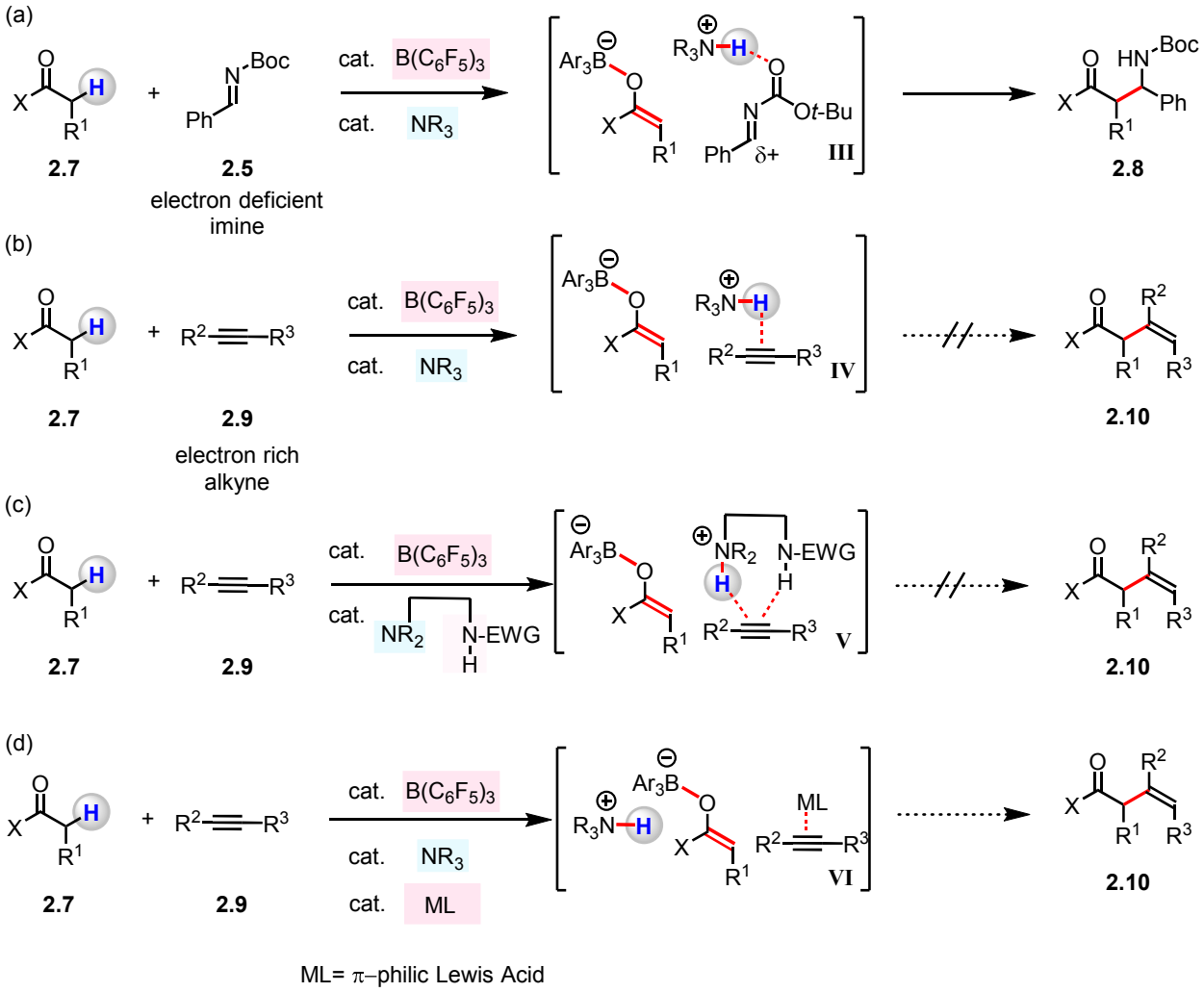
In the studies shown above, we revealed that the combination of highly Lewis acidic organoboranes and Brønsted basic amines can overcome mutual quenching and promote efficient Mannich-type reactions through the conversion of a wide variety of mono-carbonyl compounds into the corresponding enolates (**III**, Scheme 2.3a). As shown in another study (cf., Scheme 1.8, Chapter 1),[5] organoborane/NR_3-catalyzed *α*-functionalization of carbonyl compounds proceeds

[4] Shang, M.; Cao, M.; Wang, Q.; Wasa, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 13338–13526.
[5] Shang, M.; Wang, X.; Koo, S. M.; Youn, J.; Chan, J. Z.; Yao, W.; Hastings, B. T.; Wasa, M. *J. Am. Chem. Soc.* **2017**, *139*, 95–98.

through activation of the electrophiles by R_3N-derived H-bond donor catalysts (vs, Lewis activation by organoboranes; Scheme 1.6a). However, a key limitation of these methods was that the compatible electrophile was confined to *N*-Boc-benzaldemines and diazocompounds that are excellent H-bond acceptors and are highly preactivated. With less electrophilic substrates that do not possess H-bond acceptor units, the reaction did not proceed.

We became interested in further expanding the scope of FLP-catalyzed enantioselective α-functionalization reactions using weakly electrophilic substrates. In particular, we were intrigued in investing α-alkenylation of mono-carbonyl compounds **2.7** by electron rich alkyne **2.9** to produce various β,γ-unsaturated carbonyl products **2.10**. However, with the $B(C_6F_5)_3$ and a N-based Brønsted base catalyst, this desirable reaction cannot proceed because the in situ generated ammonium ion may not even recognize **2.9** (**IV**, Scheme 2.3b). For the same reason, the catalyst system comprised of $B(C_6F_5)_3$ and the bifunctional catalyst cannot promote the coupling of carbonyl pronucleophiles and alkynes (**V**, Scheme 2.3c). To overcome this major hurdle, we envisioned the incorporation of a chiral π-philic Lewis acid catalyst that is dedicated to activate alkyne **2.9** (**VI**, Scheme 2.3d). Thus, the organoborane and amine catalysts are used to convert mono-carbonyl pronuclephiles into the corresponding boron–enolates, which then undergoes enantio-determining C–C bond formation with the alkyne bound to the chiral π-philic organometallic complex may afford **2,10**, To demonstrate the proof of concept that cooperative actions of an achiral organoborane, a chiral organometallic complex and an achiral amine promotes highly enantioselective union of enolates and otherwise unreactive alkynes, we decided to investigate enantioselective Conia-ene-type reactions that involve exo-dig cyclization of alkynyl carbonyl compounds as described below.

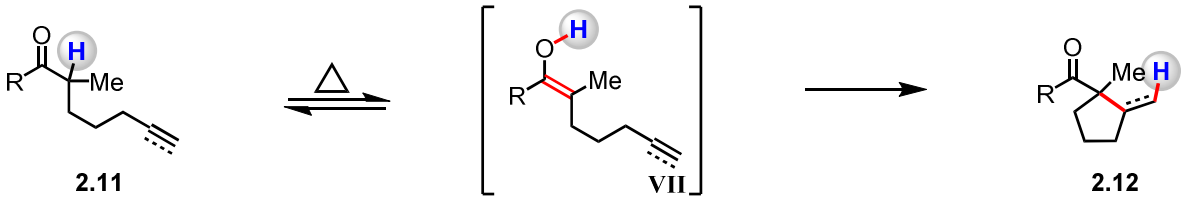
Scheme 2.3. α-Functionalization of Carbonyl Compound Promoted by Cooperative Catalysts



2.2. Background for Conia-Ene-Type Reaction

Conia-ene reaction is a class of carbonyl α-functionalization reaction that involves thermal intramolecular cyclization of enolizable carbonyl compounds with a tethered alkyne or alkene moiety leading to valuable five- or six-membered carbocycles (Scheme 2.4).[6] However, the need for over 200 ºC reaction temperature in this racemic thermal cyclization restricts its synthetic utility because functional groups that are prone to pyrolysis are incompatible under this thermal reaction conditions. To overcome this shortcoming, a significant effort has been made to promote Conia-ene-type cyclization under milder reaction condition by the use of Lewis acidic metal-based catalysts, allowing a broader applicability for this unique carbocyclization (Scheme 2.5). [7-8]

Scheme 2.4. Thermal Conia-Ene Reaction

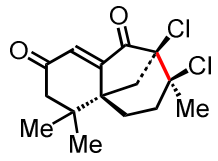


[6] (a) Conia, J. M.; Perchec, P. L. *Synthesis* **1975**, *1*, 1–19. (b) Hack, D.; Blümel, M.; Chauhan, P.; Philipps, A. R.; Enders, D. *Chem. Soc. Rev.* **2015**, *44*, 6059–6093.

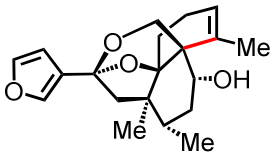
[7] For selected reports, see: (a) Ochida, A.; Ito H.; Sawamura, M. *J. Am. Chem. Soc.* **2006**, *128*, 16486–16487. (b) Zhou, C. Y.; Che, C. M. *J. Am. Chem. Soc.* **2007**, *129*, 5828–5829. (c) Gao, Q.; Zheng, B. F.; Li, J. H.; Yang, D. *Org. Lett.*, **2005**, *7*, 2185–2188. (d) Kuninobu, Y.; Kawata, A.; Takai, K. *Org. Lett.*, **2005**, *7*, 4823–4825. (e) Itoh, Y.; Tsuji, H.; Yamagata, K.; Endo, K.; Tanaka, I.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 17161–17167. (d) Takahashi, K.; Midori, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6244–6246. (e) Deng, C. L.; Song, R. J.; Liu, Y. L.; Li, J. H. *Adv. Synth. Catal.*, **2009**, *351*, 3096–3100. (f) Montel, S.; Bouyssi, D.; Balme, G. *Adv. Synth. Catal.*, **2010**, *352*, 2315–2320.

[8] For selected examples on application of Conia-ene-type reaction, see: (a) Staben, S.T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5991–5994. (b) Tsuji, H.; Yamagata, K. I.; Itoh, Y.; Endo, K.; Nakamura, M.; Nakamura, E. *Angew. Chem., Int. Ed.* **2007**, *46*, 8060–8062. (c) Takahashi, K.; Midori, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6244–6246. (d) Liu, X.; Lee, C. S. *Org. Lett.* **2012**, *14*, 2886–2889. (e) Huwyler, N.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 13066–13069. (f) Persich, P.; Llaveria, J.; Lhermet, R.; de Haro, T.; Stade, R.; Kondoh, A.; Fürstner, A. *Chem. Eur. J.* **2013**, *19*, 13047–13058. (g) Xiong, X.; Li, Y.; Lu, Z.; Wan, M.; Deng, J.; Wu, S.; Shao, H.; Li, A. *Chem. Commun.* **2014**, *50*, 5294–5297. (h) Hartrampf, F.W.; Furukawa, T.; Trauner, D. *Angew. Chem., Int. Ed.* **2017**, *56*, 893–896. (i) Ye, Q.; Qu, P.; Snyder, S. A. *J. Am. Chem. Soc.* **2017**, *139*, 18428–18431. (j) Hartrampf, F. W.; Trauner, D. *J. Org. Chem.* **2017**, *82*, 8206–8212.

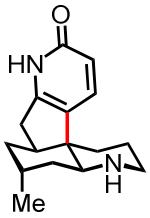
Scheme 2.5. Application of Conia-Ene-Type Cyclizations in Natural Product Synthesis



gomerone C
Carreira, E. M. **2012**



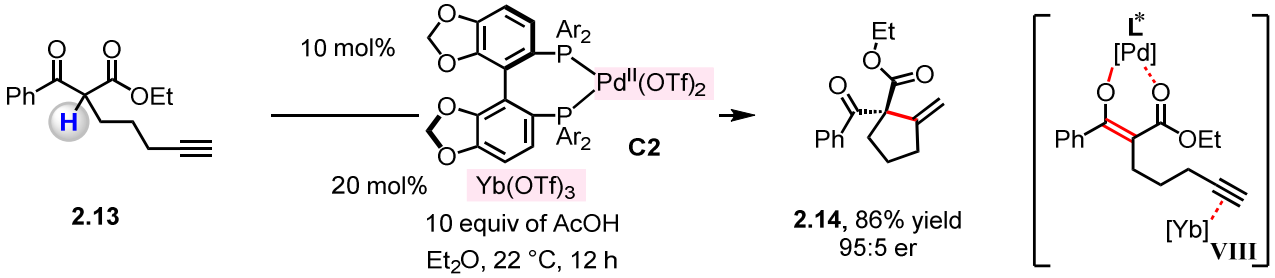
scaparvin C
Snyder, S. A. **2017**



lycoposerramine R
Trauner, D. **2017**

However, the direct catalytic stereoselective Conia-ene-type cyclizations are underdeveloped.[9] In 2005, Toste and coworkers reported the first catalytic enantioselective Conia-ene-type reaction of β-dicarbonyl compound **2.13** promoted by Pd(II) DTBM-SEGPHOS complex **C2** (Scheme 2.6).[9a] By using 20 mol% $Yb(OTf)_3$ with an excess amount acetic acid, the reaction rate can be enhanced and the desired product **2.14** can be generated in 86% yield with 95:5 er. The author proposed that the Pd-complex **C2** is responsible for the generation of nucleophilic

Scheme 2.6. Catalytic Enantioselective Conia-Ene-Type Reactions Promoted by Cooperative Lewis Acid/ Lewis Acid Catalyst System

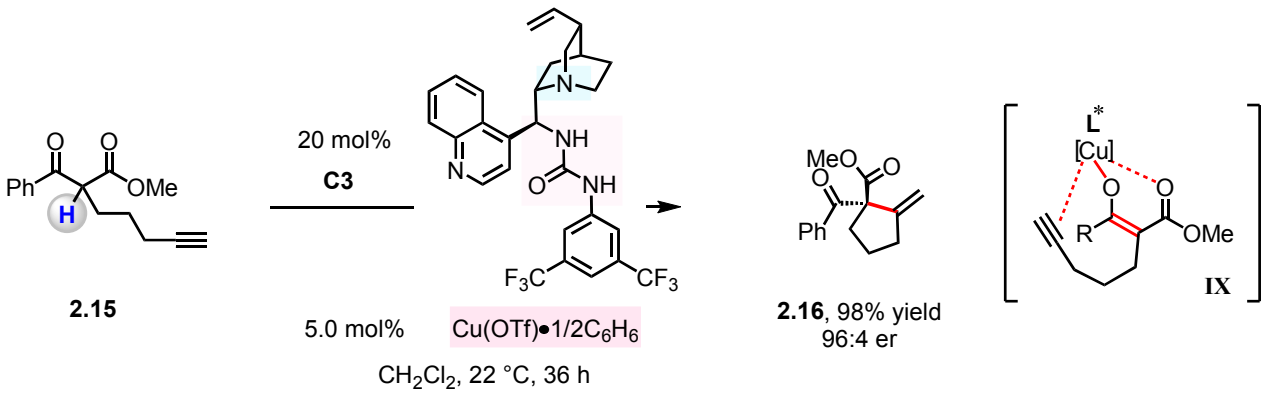


[9] For direct catalytic enantioselective Conia-ene-type reaction, see: (a) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 17168–17169. (b) Yang, T.; Ferrali, A.; Sladojevich, F.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 9140–9141. (c) Matsuzawa, A.; Mashiko, T.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2011**, *123*, 7758–7761. (d) Suzuki, S.; Tokunaga, E.; Reddy, D. S.; Matsumoto, T.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 4131–4135. (e) Shaw, S.; White, J. D. *J. Am. Chem. Soc.* **2014**, *136*, 13578–13581. (f) Blümel, M.; Hack, D.; Ronkartz, L.; Vermeeren, C.; Enders, D. *Chem. Commun*. **2017**, *53*, 3956–3959. (g) Horibe, T.; Sakakibara, M.; Hiramatsu, R.; Takeda, K.; Ishihara, K. *Angew. Chem., Int. Ed.* **2020**, *59*, 16470–16474.

palladium enolate from the 1,3-dicarbonyl compound **2.13**, which then attack Lewis acid-activated alkyne (**VIII**) to afford the cyclized product **2.14**. Although they can achieve high level of reactivity and enantioselectivity under a mild reaction conditions, this transformation requires the use of precious Pd-based catalyst, as well as readily enolizable dicarbonyl compound substrates.

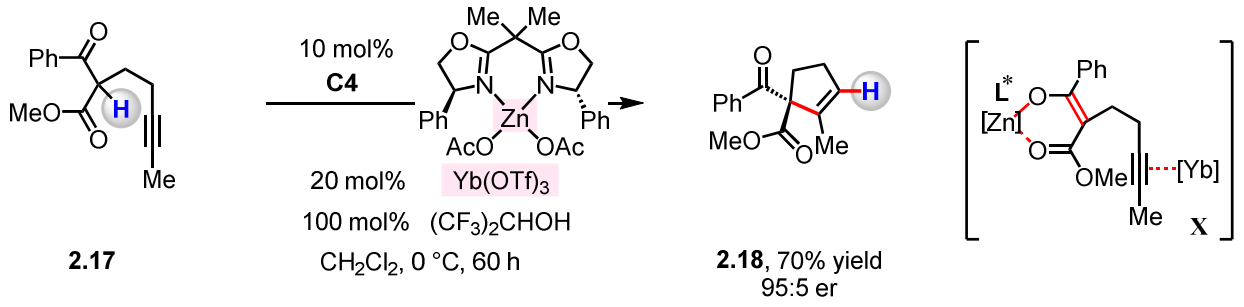
Dixon and co-workers reported an enantioselective Conia-ene-type cyclization by employing a cooperative catalyst system consisting of a Lewis acidic CuOTf and a cinchona-derived bifunctional catalyst **C3** (Scheme 2.7).[9b] With the cooperative catalyst system consisting of 5.0 mol% CuOTf and 20 mol% of **C3**, enantioselective 5-*exo*-*dig* cyclization can afford the desired product **2.16** in 98% yield with 96:4 er. Mechanistic study suggests that **C3** has two distinct roles: (1) serving as a ligand to the Cu(I) Lewis acid catalyst; (2) promoting the enolization and subsequent formation of a reactive copper enolate that would undergo *syn*-carbocupration (**IX**). Although this method does not require the use of precious metal based catalyst, the substrate scope still remains limited to the readily enolizable dicarbonyl compound.

Scheme 2.7. Lewis Acid/Brønsted Base Cooperative Catalysis in the Enantioselective Conia-Ene-Type Reaction



As discussed in Chapter 1, Shibata and co-workers disclosed the enantioselective 5-*endo-dig* cyclization promoted by the cooperative functions of Zn-PhBox complex **C4** and $Yb(OTf)_3$ (Scheme 2.8).[9d] However, this catalyst system also demands the use of readily enolizable dicarbonyl compounds.

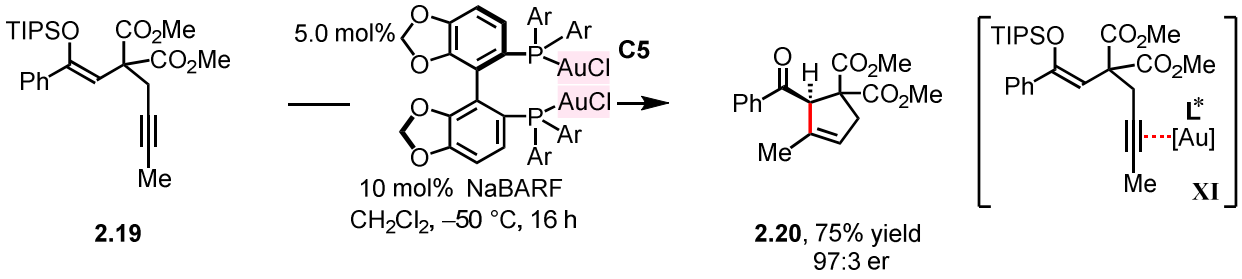
Scheme 2.8. Catalytic Enantioselective 5-*endo-dig* Carbocyclization of *β*-Ketoesters through Cooperative Functions of Chiral Zinc-based Lewis Acid and $Yb(OTf)_3$



To achieve enantioselective Conia-ene-type cyclization with monocarbonyl compounds, Toste and coworkers reported the enantioselective Conia-ene-type cyclization of silyloxy-1,5-enyne **2.19** promoted by chiral Au complex **C5** (Scheme 2.9).[10-11] The desired ketone substituted cyclopetene derived product **2.20** can be obtained in 75% yield with 97:3 er. The enantioselective 5-*endo-dig* cyclization occurs between the nucleophilic silicon enolate and **C5**-activated alkyne (**XI**). Although monocarbonyl compound derived Conia-ene-type cyclization product can be obtained with high yield and enantioselectivity, the requirement for the use of preformed silicon enolates that contains sterically hindered gem-substituents to induce Thorpe-Ingold effect severely limits the application of this method. Furthermore, this method requires the use of precious Au-based catalyst.

[10] Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2764–2765.
[11] Brazeau, J. F.; Zhang, S.; Colomer, I.; Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 2742–2749.

Scheme 2.9. Enantioselective Cyclizations of Silyloxyenynes Catalyzed by Au Complex



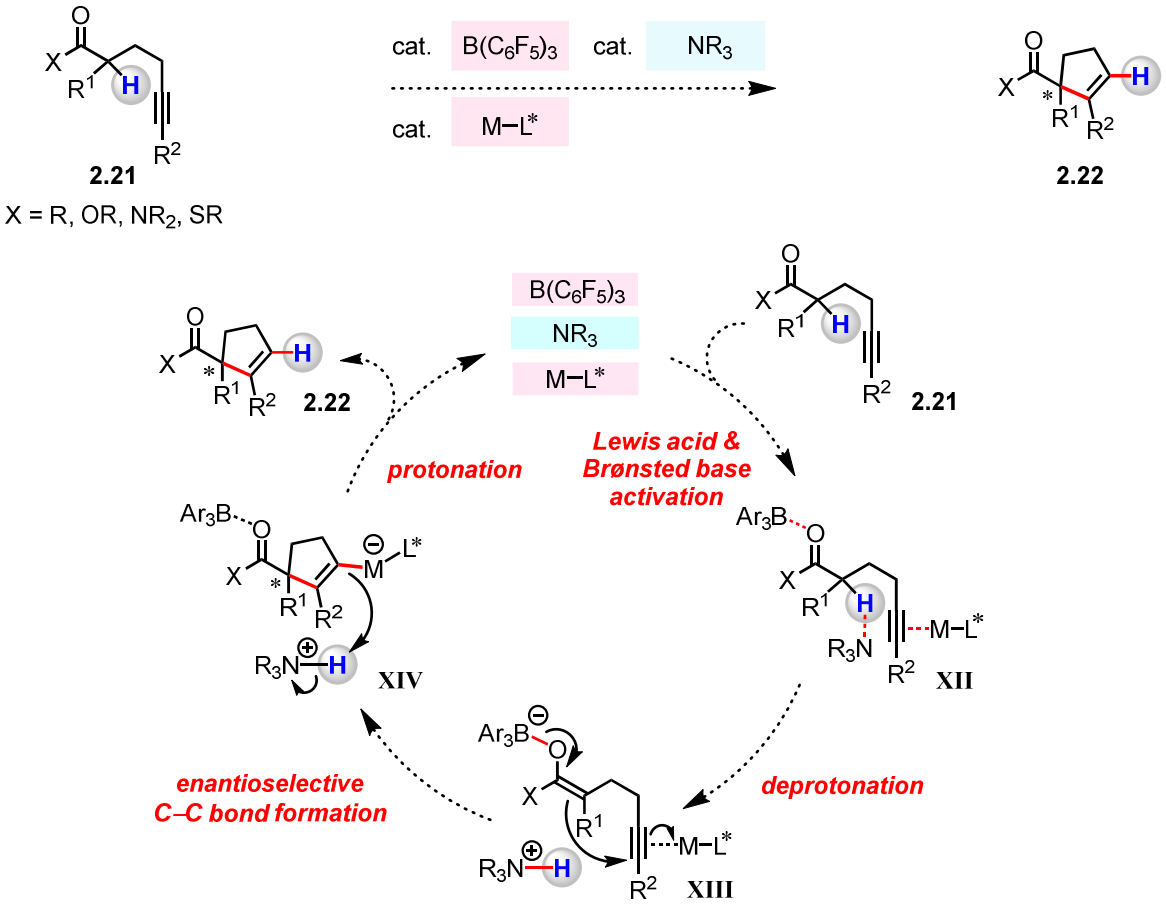
As the aforementioned literature precedents have shown, cooperative catalyst systems that promote direct catalytic enantioselective Conia-ene-type processes with mono-carbonyl compounds remain unprecedented. This is mainly because these catalyst systems are not compatible with Brønsted basic catalysts (e.g., DBU, Barton's base) that may be capable of deprotonating the desirable mono-carbonyl substrates due to the undesirable acid/base complexation.

2.3. Our Approach

Since we have shown that the combination of borane Lewis acid and *N*-alkylamine Brønsted base can overcome mutual quenching and work cooperatively to activate a wide variety of mono-carbonyl compounds to generate boron enolate, we proposed that by incorporating a π-philic Lewis acid co-catalyst that could selectively activate the alkyne moiety, the direct enantioselective Conia-ene-type cyclization between mono-carbonyl and alkyne moieties can then be achieved (Scheme 2.10). The basic *N*-alkylamine could deprotonate $B(C_6F_5)_3$ activated carbonyl compound, generating a boron enolate and an ammonium ion **XIII**. In the meantime, a chiral Lewis acid co-catalyst (M-L*) could activate the alkyne unit. Then the stereoselective C–C bond formation between the boron enolate and alkyne would deliver the intermediate **XIV**. Subsequent protonation of alkenyl M-L* bond by the in situ generated ammonium ion would afford the desired cyclopentenyl product **2.22**.

One key advantage provided by this untethered cooperative catalyst system is that efficiency and stereoselectivity can be optimized through rapid evaluation of readily accessible Lewis acids, chiral ligands, and *N*-alkylamines. However, the two Lewis acids may undergo mutual quenching with the Brønsted base catalyst. Furthermore, the two Lewis acid catalysts, $B(C_6F_5)_3$ and M-L*, may have overlapping functions for activation of carbonyl and alkyne moieties which may lead to racemic background reaction. Therefore, we need to find the right catalyst combination that can overcome these challenges and promote highly enantioselective Conia-ene-type reaction with monocarbonyl compounds.

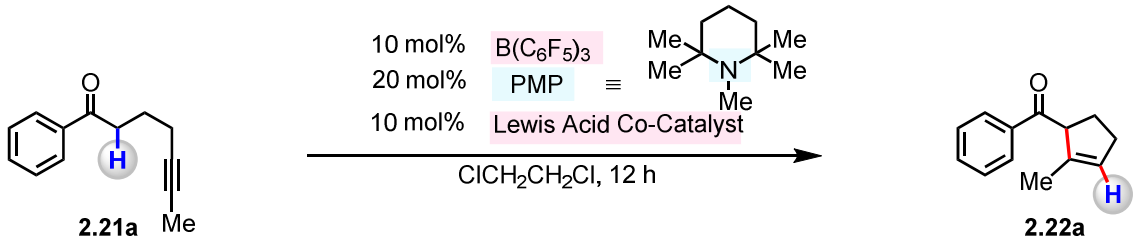
Scheme 2.10. Enantioselective Conia-Ene-Type Cyclization and Proposed Catalytic Cycle



2.4. Results and Discussion

To begin the initial investigation, the transformation involving the substrate 1-phenylhept-5-yn-1-one **2.21a** was evaluated using $B(C_6F_5)_3$, 1,2,2,6,6-pentamethylpiperidine (PMP), and various Lewis acid co-catalysts[4-6, 8], which are known to activate the alkyne moieties, as potential catalyst combinations. We found that with 10 mol% $B(C_6F_5)_3$, 20 mol% PMP, and Au-based Lewis acid or Zn-based Lewis acid, the reaction with **2.21a** in $ClCH_2CH_2Cl$ (DCE) at 80 °C would afford **2.22a** in up to >95 % yield (Table 2.1, entry 1-13). However, when the reaction was carried out at 22 °C, only ZnI_2 co-catalyst afforded the desired product **2.22a** in quantitative yield (entry 16). The use of Zn-based Lewis acid catalyst is more preferable compared to the expensive Au-based Lewis acid catalyst. Furthermore, various Zn-based Lewis acid ligand complex catalyzed enantioselective transformations have been developed, which can provide us more opportunities to achieve the enantioselective Conia-ene-type transformation. With the optimal catalyst combination in hand, we carried out control experiments and further optimization studies (Table 2.2). As the control experiment results show, all three catalysts, $B(C_6F_5)_3$, PMP and ZnI_2 are required in order to obtain the desired product (entry 1-4). This suggests the Lewis acid $B(C_6F_5)_3$, Brønsted base PMP and Lewis acid co-catalyst ZnI_2 work cooperatively to promote the Conia-ene-type cyclization. After further optimization of reaction condition, the desired product was obtained in quantitative yield with 5.0 mol% $B(C_6F_5)_3$, 10 mol% PMP, and 5.0 mol% ZnI_2 in CH_2Cl_2 (entry 5). Since that we have found out the optimal catalyst combination and reaction condition, the enantioselective transformation was then investigated.

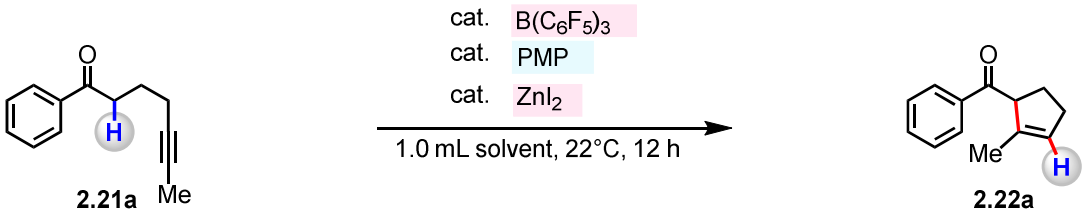
Table 2.1. Evaluation of Lewis Acid Co-Catalyst [a,b]



entry	Lewis Acid Co-Catalyst	Reaction temperature (°C)	yield of **2.22a** (%)
1	AgOTf	80	16
2	$Mg(OTf)_2$	80	0
3	$In(OTf)_3$	80	13
4	$Yb(OTf)_3$	80	0
5	CuOTf	80	15
6	$[Cu(OTf)_2]_2 \bullet C_6H_6$	80	18
7	$AuPPh_3Cl/AgOTf$	80	40
8	$AuPPh_3Cl$	80	>95
9	$Zn(OTf)_2$	80	64
10	$ZnCl_2$	80	>95
11	ZnI_2	80	>95
12	$Zn(OAc)_2$	80	>95
13	$Zn(NTf_2)_2$	80	0
14	$AuPPh_3Cl$	22	0
15	$ZnCl_2$	22	78
16	ZnI_2	22	>95
17	$Zn(OAc)_2$	22	15

[a] Conditions: 1-phenylhept-5-yn-1-one (**2.21a,** 0.2 mmol), $B(C_6F_5)_3$ (10 mol%), 1,2,2,6,6-pentamethylpiperidine (20 mol%), Lewis Acid Co-Catalyst (10 mol%), $ClCH_2CH_2Cl$ (1.0 mL), under N_2, 80 or 22 °C, 12 h. [b] Yield was determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard.

Table 2.2. Evaluation of Reaction Conditions and Control Experiments



2.21a **2.22a**

entry	$B(C_6F_5)_3$ (mol%)	PMP (mol%)	ZnI_2 (mol%)	solvent	yield of **2.22a** (%)
1	10	20	10	CH_2Cl_2	>95
2	10	none	10	CH_2Cl_2	<5
3	none	20	10	CH_2Cl_2	0
4	10	20	none	CH_2Cl_2	0
5	5	10	5	CH_2Cl_2	>95
6	10	20	10	$ClCH_2CH_2Cl$	>95
7	10	20	10	THF	5
8	10	20	10	Toluene	80

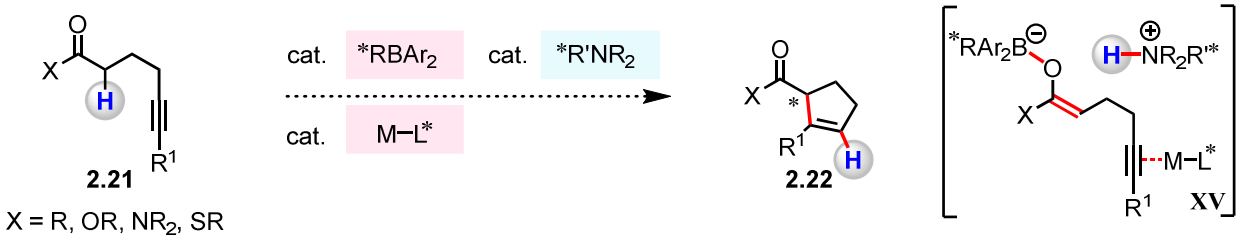
[a] Conditions: 1-phenylhept-5-yn-1-one (**2.21a,** 0.2 mmol), $B(C_6F_5)_3$, 1,2,2,6,6-pentamethylpiperidine, ZnI_2 , solvent (1.0 mL), under N_2, 22 °C, 12 h. [b] Yield was determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard.

In this Lewis acid, Brønsted base, Lewis acid co-catalyst system, the three catalysts are not tethered together, we can easily and independently modify the catalyst structure to achieve highly enantioselective reaction.[10] The enantioselective transformation can be achieved through either using chiral organoboron catalyst, chiral Brønsted base, chiral Lewis acid co-catalyst, or using any of these three chiral catalysts in combination (Scheme 2.11).

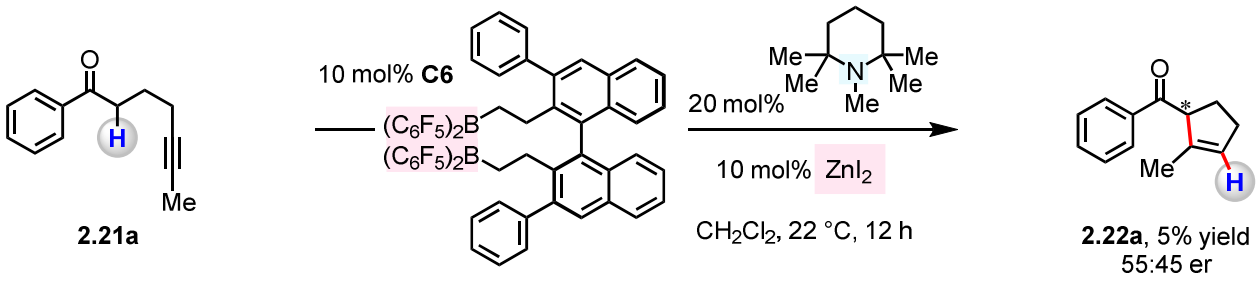
Since the chiral boron Lewis acid is forming a covalent bond to the substrate, this could promote a better control of enantioselectivity. To test this hypothesis, we first evaluated the chiral organoboron catalyst **C6**, PMP and ZnI_2 catalyst system. However, with the substrate **2.21a,** the desired product can only be obtained in about 5% yield with 55:45 er (Scheme 2.12). Both the

reaction efficiency and enantioselectivity is not promising and synthesis and optimization of the chiral organoboron structure would be cumbersome. Thus, we decided to investigate the chiral Lewis acid co-catalyst approach, which allows us to rapidly evaluate readily available metal ligand combinations to achieve the highly enantioselective Conia-ene-type cyclization.[12]

Scheme 2.11. Enantioselective Conia-Ene-Type Cyclization



Scheme 2.12. Enantioselective Conia-Ene-Type Cyclization Promoted by Chiral Organoborane, *N*-alkylamine and ZnI_2

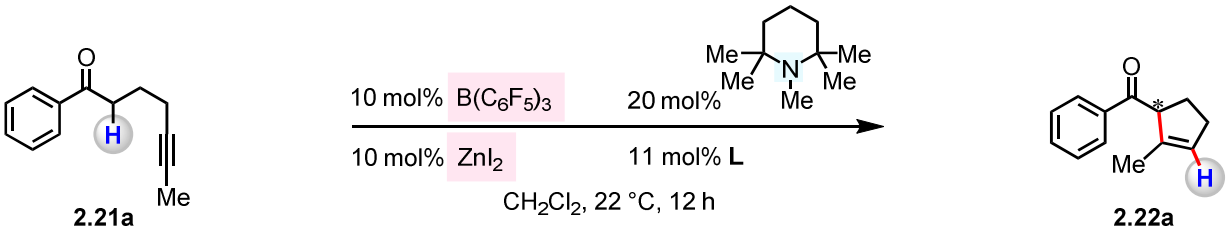


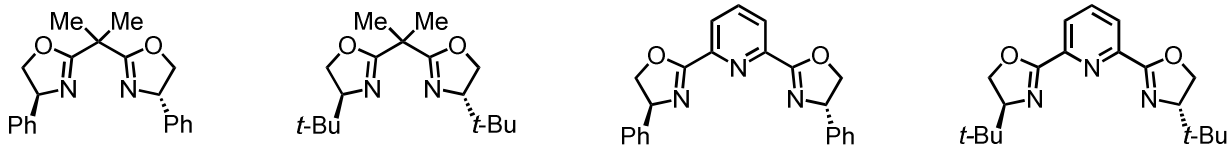
To identify an optimal metal/ligand combination, we probed the ability of $B(C_6F_5)_3$, PMP, and various chiral Lewis acid/ligand complexes to catalyze the cyclization of 1-phenylhept-5-yn-1-one **2.21a** (CH_2Cl_2, 12 h, 22 °C), to generate **2.22a**. Various representative bisoxazoline ligands

[12] Foe selected reviews, see: (a) Wu, X. F.; Neumann, H. *Adv. Synth. Catal.*, **2009**, *354*, 3141–3160. (b) Łowicki, D.; Baś, S.; Mlynarski, J. *Tetrahedron* **2015**, *71*, 1339–1394. (c) Baś, S.; Szewczyk, M.; Mlynarski, J. in *Chiral Lewis Acids in Organic Synthesis*, Mlynarski, J., Eds.; Wiley-VCH: 2017; Chapter 5. (d) Trost, B. M.; Hung, C. I.; Mata, G. *Angew. Chem., Int. Ed.* **2020**, *59*, 4240-4261.

were evaluated; PhPybox Ligand **L3** can give the desired product in highest enantioselectivity 72:28 er (Table 2.3).

Table 2.3. Ligand Optimization for the 1-Phenylhept-5-yn-1-one Substrate [a,b]





L1	L2	L3	L4
2.22a,72% yield 68:32 er	**2.22a**, 58% yield 57:43 er	**2.22a**, 46% yield 72:28 er	**2.22a**, >95% yield 66:34 er

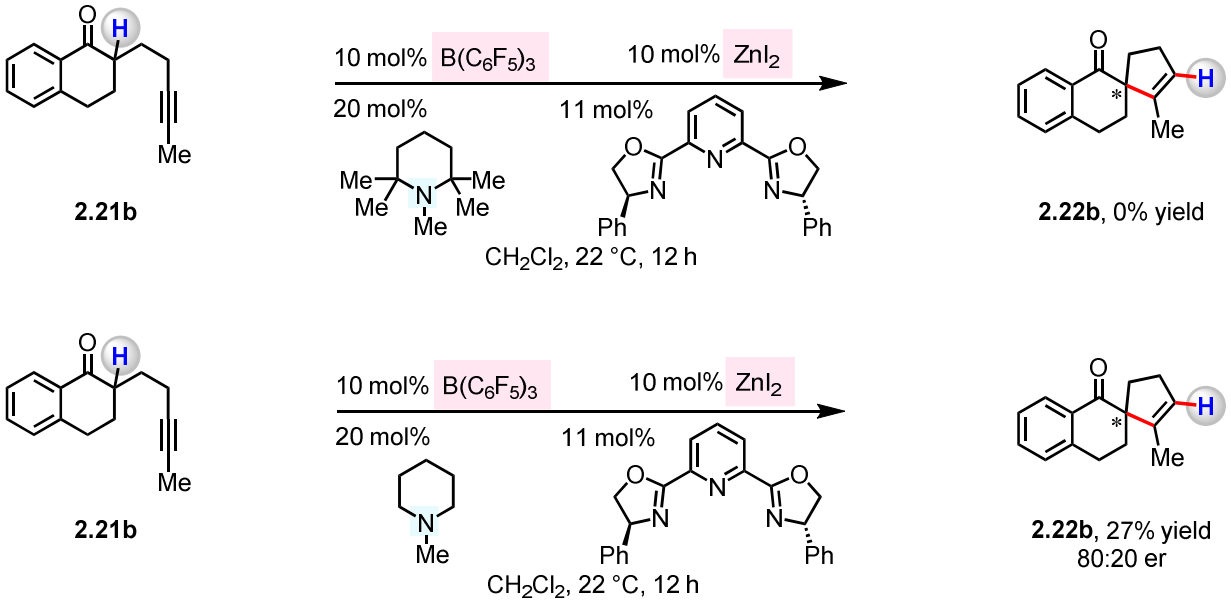
[a] Conditions: 1-phenylhept-5-yn-1-one (**2.21a,** 0.2 mmol), $B(C_6F_5)_3$ (10 mol%), 1,2,2,6,6-pentamethylpiperidine (20 mol%), ZnI_2 (10 mol%), bis-oxazoline ligand (11 mol%), CH_2Cl_2 (1.0 mL), under N_2, 22 °C, 12 h. [b] Yield was determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. The er values were determined by HPLC analysis of the purified product.

However, the enantioselectivity could not be further improved with this substrate. Based on the proposed catalytic cycle (Scheme 2.10), we have several hypotheses. First, the desired product **2.22a**, which still contains an acidic α-proton may undergo racemization. Second, the in situ generated boron enolate (**XIII**) may isomerize to give Z/E mixture. In addition, the methyl group in the **2.21a** may not be large enough for the catalyst to differentiate between substitutes on the alkyne to form a rigid Zn–Alkyne complex (**XII**). To test these hypotheses, we designed and evaluated several substrates.

Firstly, α-tetralone derived substrate **2.21b** was evaluated because it would only afford Z-boron enolate (Scheme 2.13). In addition, the desired product **2.22b** does not contain α-C–H proton so it would not undergo racemization. However, with the standard reaction condition, the

desired product was not obtained. We hypothesized that with the more hindered substrate **2.21b** that contain tertiary α-C–H bond, the PMP may be too sterically hindered for the deprotonation process (Scheme 2.10, **XII** → **XIII**). Therefore, less hindered *N*-alkyl amine Brønsted bases were evaluated for this substrate, *N*-methyl piperidine was found to give the desired product in 27% yield with 80:20 er. These results suggest that the racemization of the product and isomerization of boron enolate may not be the reason for the low enantioselectivity.

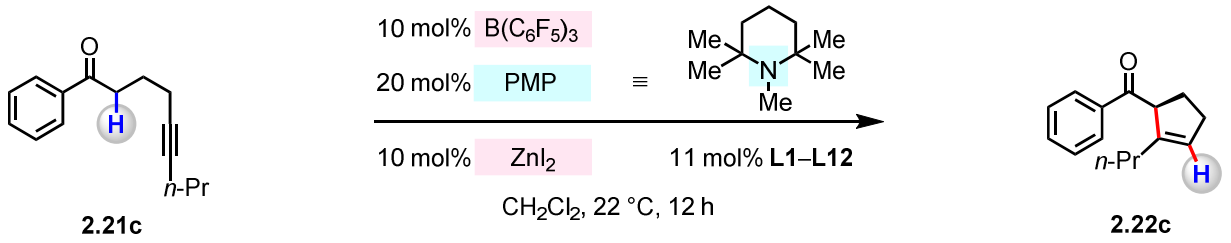
Scheme 2.13. Enantioselective Conia-Ene-Type Cyclization with Tetralne Derived Substrate

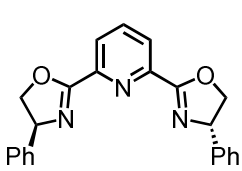


To test the third hypothesis, 1-phenylnon-5-yn-1-one **2.21c** was evaluated (Table 2.4). This substrate has a more sizable *n*-Pr substituent and may have better steric interaction with M-L*. The combination of 10 mol% ZnI_2 and Ph–PyBOX (**L3**) or Ph–DBFOX (**L5**) afforded **2.22c** in 20% and 7% yield, and 83:17 and 55:45 er, respectively. With Ph–BOX (**L1**) as the ligand, the desired product was generated in >95% yield and 89:11 er. It seems that steric interaction between the Zn/ligand complex and substituent in the alkyne moiety can help improve the enantioselectivity. Catalysts derived from alkyl-substituted **L6** (10% yield and 75:25 er) and **L2**

(6% yield, 71:28 er) were less effective. We proposed that by tuning the bite angle of the Ph–BOX ligand, it may have better steric interaction between the substituent and Zn/ligand complex which may further improve the enantioselectivity. Therefore, Ph–BOX ligands with varying 2,2'-substiutents (cyclopropyl (**L7**), diisopropyl (**L8**), dicyclopentyl (**L9**) and dibenzyl (**L10**)) were

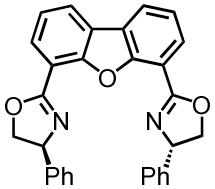
Table 2.4. Evaluation of Bis-oxazoline Ligands for 1-Phenylnon-5-yn-1-one Substrate [a,b]





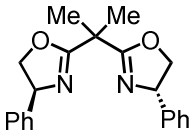
L3

2.22c, 20% yield
83:17 er



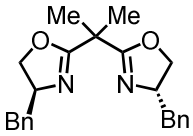
L5

2.22c, 7% yield
55:45 er



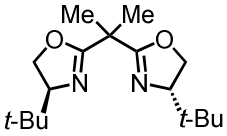
L1

2.22c, >95% yield
89:11 er



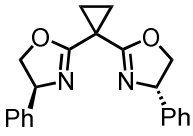
L6

2.22c, 10% yield
75:25 er



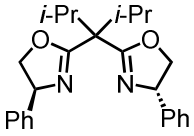
L2

2.22c, 6% yield
71:28 er



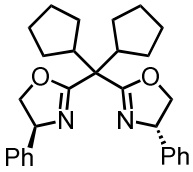
L7

2.22c, 85% yield
85:15 er



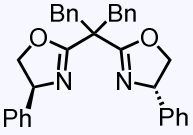
L8

2.22c, >95% yield
93:7 er



L9

2a, >95% yield
93:7 er

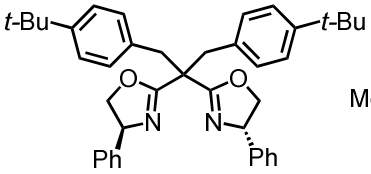


L10

2.22c, >95% yield
97:3 er

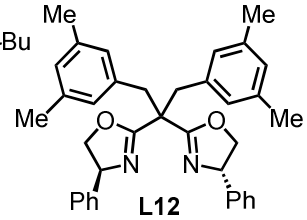
with 8.0 mol% **L10**:
2.22c, >95% yield
92:8 er

with 13 mol% **L10**:
2.22c, <5% yield
97:3 er



L11

2.22c, >95% yield
96:4 er



L12

2.22c, >95% yield
97:3 er

[a] Conditions: 1-phenylnon-5-yn-1-one (**2.21c**, 0.2 mmol), $B(C_6F_5)_3$ (10 mol%), 1,2,2,6,6-pentamethylpiperidine (20 mol%), ZnI_2 (10 mol%), bis-oxazoline ligand (11 mol%), CH_2Cl_2 (1.0 mL), under N_2, 22 °C, 12 h. [b] Yield was determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. The er values were determined by HPLC analysis of the purified product.

then evaluated. We found that dibenzyl substituted **L10** (large bite angle and better steric interaction) is the most effective ligand, providing **2.22c** in >95 % yield with 97:3 er. Further evaluation of more sterically hindered ligand **L11** and **L12** does not lead to the further improvement on the enantioselectivity.

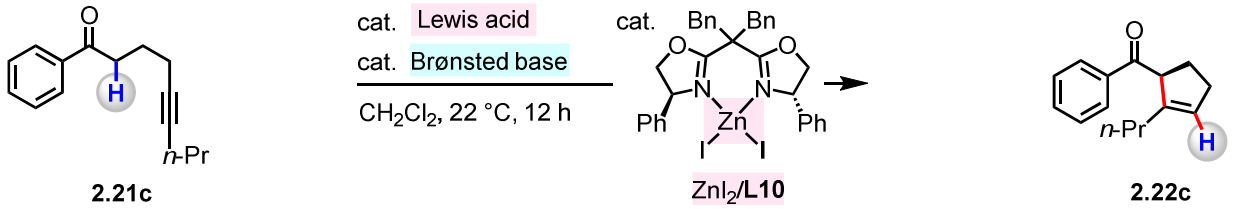
We also found that the loading of a bis-oxazoline ligand is essential on reaction efficiency and enantioselectivity. In the absence of **L10**, *rac*-**2.22c** can be isolated in >95% yield, when 10 mol% of ZnI_2 and 8.0 mol% of **L10** was used, the enantioselectivity of **2.22c** decreased to 92:8 er which may be due to the racemic background reaction. However, when excess **L10** was used (13 mol%), **2.22c** was obtained in <5% yield. This suggests that the Lewis basic oxazoline units of **L10** can deactivate $B(C_6F_5)_3$. Therefore, preformed and purified ZnI_2/**L10** complex was used which gave us the desired product in similar yield and enantioselectivity.[13-14]

With the optimal ZnI_2/ligand combination in hand, we then set out to identify the optimal organoborane and Brønsted base catalysts, and optimize the reaction parameters (Table 2.5). With Et_3N, the desired product **2.22c** was obtained in >95% yield and 97:3 er (entry 1); however, with DBU as the base, none of the desired product could be detected (entry 2). With less $B(C_6F_5)_3$ (7.5 mol%), PMP (15 mol%), and ZnI_2/**L10** (7.5 mol%), efficiency decreased but enantioselectivity remained the same (90% yield, 97:3 er; entry 4). The reaction efficiency improved at 40 °C (entry 5), allowing catalyst loading to be reduced to 5.0 mol% $B(C_6F_5)_3$, 10 mol% PMP and 5.0 mol% ZnI_2/**L10**; under these conditions, **2.22c** was produced in 92% yield and 97:3 er (entry 6). Control experiments showed that in the absence of the Brønsted base, the organoborane catalyst, or the ZnI_2/**L10**, no desired product was obtained (entries 7–9); when the sterically less hindered BF_3•OEt_2 or the less Lewis acidic BPh_3 were used, no desired product was obtained (entries 10–11). Thus, the appropriately Lewis acidic and sterically hindered $B(C_6F_5)_3$, PMP, together with ZnI_2/**L10** complex emerged as the most effective combination for this enantioselective Conia-ene-type cyclization. Furthermore, no racemization was observed when we treated the enantioenriched

[13] Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2002**, *8*, 1888–1898.
[14] Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2011**, *111*, 284–437.

desired product **2.22c** with the standard reaction conditions. It is probably because the unfavorable streic interaction between the n-Pr and Ph substituents makes **2.22c** hard to be deprotonated.

Table 2.5. Evaluation of Enantioselective Reaction Conditions and Control Experiments [a,b,c]



2.21c — ZnI_2/**L10** — **2.22c**

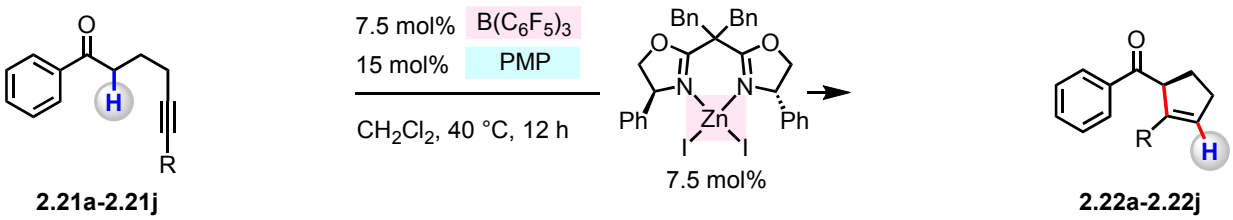
entry	Lewis acid (mol%)	Brønsted base (mol%)	ZnI_2/**L9** (mol%)	yield of **2.22c** (%)	er
1	$B(C_6F_5)_3$ (10)	NEt_3 (20)	10	>95	97:3
2	$B(C_6F_5)_3$ (10)	DBU (20)	10	0	ND
3	$B(C_6F_5)_3$ (10)	PMP (20)	10	>95	97:3
4	$B(C_6F_5)_3$ (7.5)	PMP (15)	7.5	90	97:3
5[c]	$B(C_6F_5)_3$ (7.5)	PMP (15)	7.5	>95	97:3
6[c]	$B(C_6F_5)_3$ (5.0)	PMP (10)	5.0	92	97:3
7	$B(C_6F_5)_3$ (5.0)	none	5.0	0	ND
8	none	PMP (10)	5.0	0	ND
9	$B(C_6F_5)_3$ (5.0)	PMP (10)	0	0	ND
10	BF_3•OEt_2 (5.0)	PMP (10)	5.0	0	ND
11	BPh_3 (5.0)	PMP (10)	5.0	0	ND

[a] Conditions: 1-phenylnon-5-yn-1-one (**2.21c**, 0.2 mmol), organoborane, Brønsted base, ZnI_2/**L10** complex, CH_2Cl_2 (1.0 mL), under N_2, 22 °C, 12 h. [b] Yield was determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. The er values were determined by HPLC analysis of the purified product. [c] The reaction mixture was allowed to stir at 40 °C.

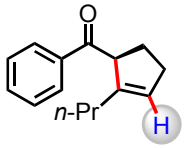
Having established the most effective catalyst combination and reaction condition, we have demonstrated this synthetic protocol can be applied to a variety of 1-phenyl ketones with different alkyne substituents for the enantioselective Conia-ene-type reaction (**2.21a**–**2.21j**; Table 2.6). With 1-phenylhex-5-yn-1-one, containing a terminal alkyne moiety (R = H), the transformation

was inefficient and moderately enantioselective (10% yield, 70:30 er). In contrast, when 1-phenylhept-5-yn-1-one was evaluated, which bears an internal alkyne (R = Me), the desired

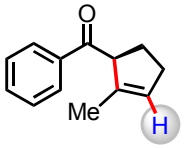
Table 2.6 Conia-Ene-Type Reactions with Different Alkyne Substituents [a,b]



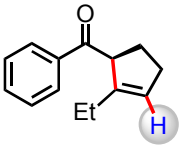
2.21a-2.21j **2.22a-2.22j**



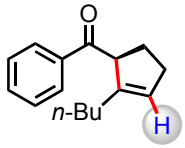
2.22c, 98% yield
97:3 er



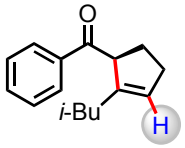
2.22a, 96% yield
82:18 er



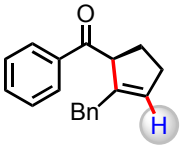
2.22d, 95% yield
96:4 er



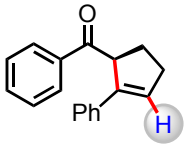
2.22e, 99% yield
97:3 er



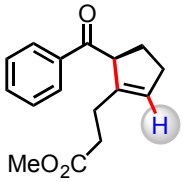
2.22f, 97% yield[c]
96:4 er



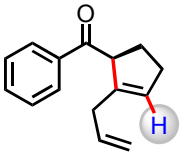
2.22g, 82% yield[c]
98:2 er



2.22h, 50% yield[c]
91:9 er



2.22i, 97% yield
94:6 er



2.22j, 94% yield
97:3 er

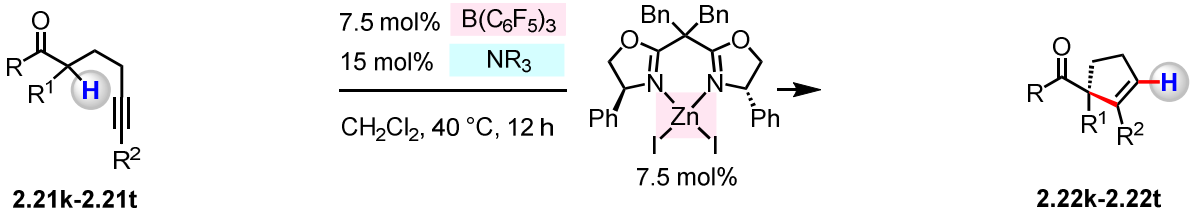
[a] Conditions: Alkynl ketone (**2.21a**-**2.21e**, **2.21i**, **2.21j**, 0.2 mmol), $B(C_6F_5)_3$ (7.5 mol%), 1,2,2,6,6-pentamethylpiperidine (15 mol%), ZnI_2/**L10** (7.5 mol%), CH_2Cl_2 (1.0 mL), under N_2, 40 °C, 12 h. [b] Yield of isolated and purified product. The er values were determined by HPLC analysis of the purified product. [c] Alkynl ketone (**2.21f**-**2.21h**, 0.2 mmol), $B(C_6F_5)_3$ (10 mol%), 1,2,2,6,6-pentamethylpiperidine (20 mol%), ZnI2/**L10** (10 mol%), $ClCH_2CH_2Cl$ (1.0 mL), under N_2, 60 °C, 24 h.

product **2.22a** can be obtained in 96% yield and 82:18 er. For substrates that carry a larger ethyl, *n*-propyl, *n*-butyl, and *iso*-butyl substituent, we are able to obtain the desired products in >95% yield and 96:4–97:3 er (**2.22c**–**2.22f**). This is in consistent with the hypothesis that the steric interaction between the alkyne substituents and M-L* complex could help improve the enantioselectivity. Although, with higher reaction temperature, benzyl-substituted substrate furnished **2.22g** in 82% yield and 98:2 er, phenyl-substituted substrate was less efficient (**2.22h**, 50% yield, 91:9 er). These results implied that large steric hindrance of the alkyne substituents impeded the reaction efficiency. We also demonstrated the presence of a carboxylic ester or a monosubstituted alkene is tolerated (**2.22i** and **2.22j**). The desired product can be obtained in up to 97% yield and 97:3 er.

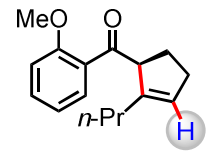
Since we have shown various alkyne substituents are compatible for this enantioselective transformation, we then investigated reactions with different aryl- and alkyl-substituted ketones (Table 2.7). 2-Methoxyphenyl- and 4-bromophenyl-substituted ketones gave **2.22k** (95% yield, 93:7 er) and **2.22l** (97% yield, 97:3 er), respectively. The process involving indanone derivative or tetralone derivative did not afford desired product when PMP was employed as a Brønsted base catalyst. We hypothesize that because it is too hindered for PMP to deprotonate α tertiary C–H bond within a $B(C_6F_5)_3$-activated ketone. After evaluation of various Brønsted base catalyst, less sterically hindered 1-methylpiperidine was found to deliver the desired product which contains fully substituted stereogenic center. **2.22m** was produced in 98% yield and 99:1 er. Tetralone-derived **2.22n** was formed inefficiently (20% yield, 98:2 er) even in 60 °C for 24 hours. Perhaps indicating severe steric repulsion between the *n*-propyl substituent and the tetralone ring. Thus, when less steric hindered Me-substituted substrate **2.21b** was employed, the desired product can be obtained in 73% yield. However, the enantioselectivity decreased to 91:9 er. Heteroaryl-

substituted substrates are also compatible, which gave us **2.22o** (99% yield, 98:2 er) and **2.22p** (99% yield, 97:3 er). In addition, alkyl substituted ketones were also found to give the desired product in similar efficiency as represented by **2.22q** (91% yield, 95:5 er) and **2.22r** (77% yield, 96:4 er). However, bicyclic product **2.22s** was generated with 1-methylpiperidine as the Brønsted base, but in diminished er (82% yield, 80:20 er).

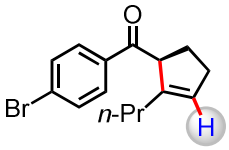
Table 2.7. Conia-Ene-Type Reactions with Different Ketones [a,b]



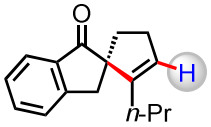
2.21k-2.21t → **2.22k-2.22t**



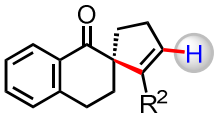
2.22k, 95% yield
93:7 er



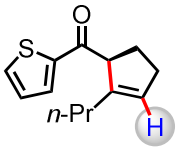
2.22l, 97% yield
97:3 er



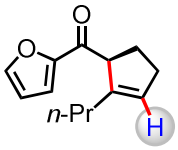
2.22m, 98% yield[c]
99:1 er



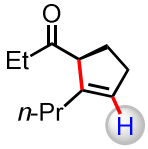
2.22n (R^2 = *n*-Pr)[c,d]
20% yield, 98:2 er
2.22b (R^2 = Me)[c,d]
73% yield, 91:9 er



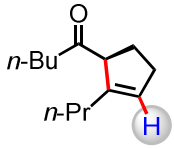
2.22o, 99% yield
98:2 er



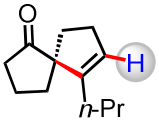
2.22p, 99% yield
97:3 er



2.22q, 91% yield
95:5 er



2.22r, 77% yield
96:4 er

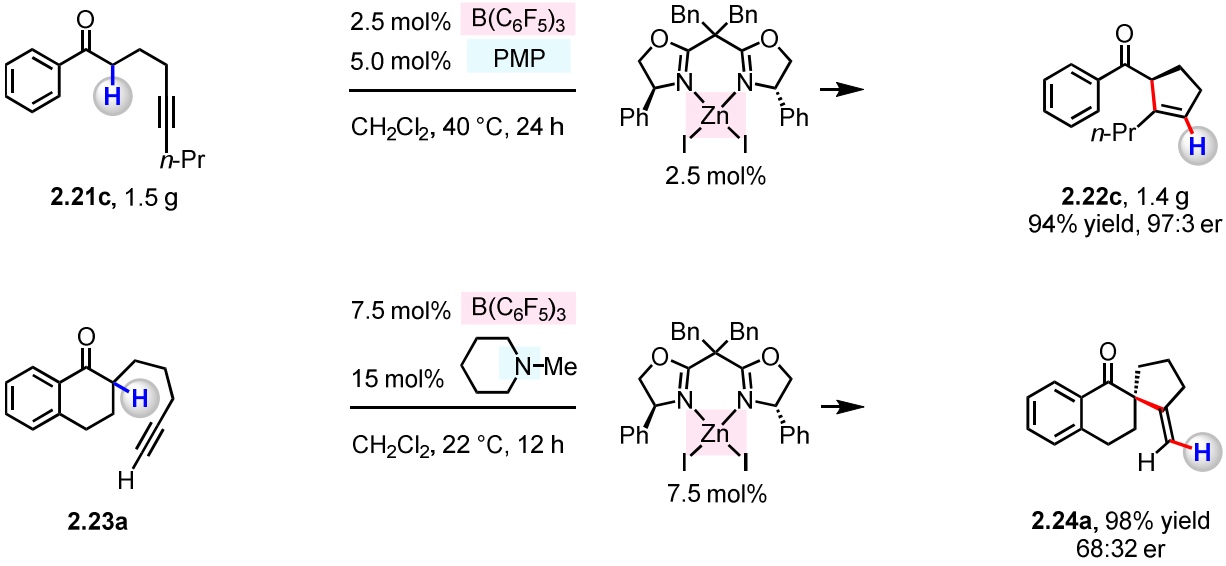


2.22s, 82% yield[c]
80:20 er

[a] Conditions: Alkynl ketone (**2.21b, 2.21k-2.21m, 2.21o-2.21s**, 0.2 mmol), $B(C_6F_5)_3$ (7.5 mol%), 1,2,2,6,6-pentamethylpiperidine (15 mol%), ZnI_2/**L10** (7.5 mol%), CH_2Cl_2 (1.0 mL), under N_2, 40 °C, 12 h. [b] Yield of isolated and purified product. The er values were determined by HPLC analysis of the purified product. [c] 1-Methylpiperidine was used as a Brønsted base catalyst. [d] Alkynl ketone (**2.21b, 2.21n,** 0.2 mmol), $B(C_6F_5)_3$ (10 mol%), 1-methylpiperidine (20 mol%), ZnI2/**L10** (10 mol%), $ClCH_2CH_2Cl$ (1.0 mL), under N_2, 60 °C, 24 h.

The method is also readily scalable. Treatment of 1.5 g (7.0 mmol) of **2.21c** with 2.5 mol% $B(C_6F_5)_3$, 5.0 mol% PMP, and 2.5 mol% ZnI_2/**L10** (CH_2Cl_2, 24 h, 40 °C) afforded **2.22c** in 94% yield (6.6 mmol, 1.4 g) and 97:3 er (Scheme 2.14). Moreover, this cooperative catalyst system can also promote 5-*exo-dig* cyclization. We discovered that cycloaddition of 1-phenylhept-6-yn-1-one **2.23a** (5-*exo-dig*) is facilitated by $B(C_6F_5)_3$, 1-methylpiperidine. and ZnI_2/**L10** to deliver *exo*-methylene-substituted cyclopentane **2.23b** in 98% yield but just 68:32 er. The low enantioselectivity is probably due to the fact that there is not enough steric interaction between the terminal alkyne and ZnI_2/**L10** complex. In order to further improve enantioselectivity for the 5-*exo-dig* cyclization, further optimization of the M-L* combination is still required.

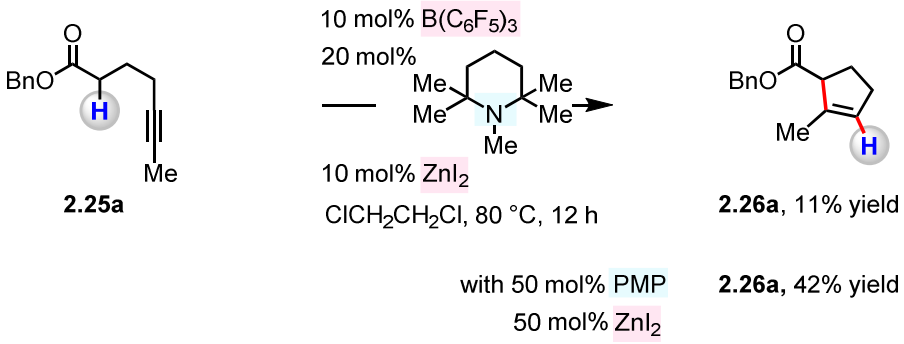
Scheme 2.14. Scale-up Experiments and 5-*exo-dig* Cycloaddition



Now that we have demonstrated that we can achieve the direct enantioselective Conia-ene-type cyclization with broad scope of alkynyl ketones, we then went to investigate the reactivity with ester derived substrate **2.25a** which is harder to be deprotonated to generate the corresponding enolate (Scheme 2.15). Treatment of **2.25a** with 10 mol% $B(C_6F_5)_3$, 20 mol% PMP, and 10 mol% ZnI_2 ($ClCH_2CH_2Cl$, 12 h, 80 °C) afforded **2.26a** in only 11% yield. Further optimization of the

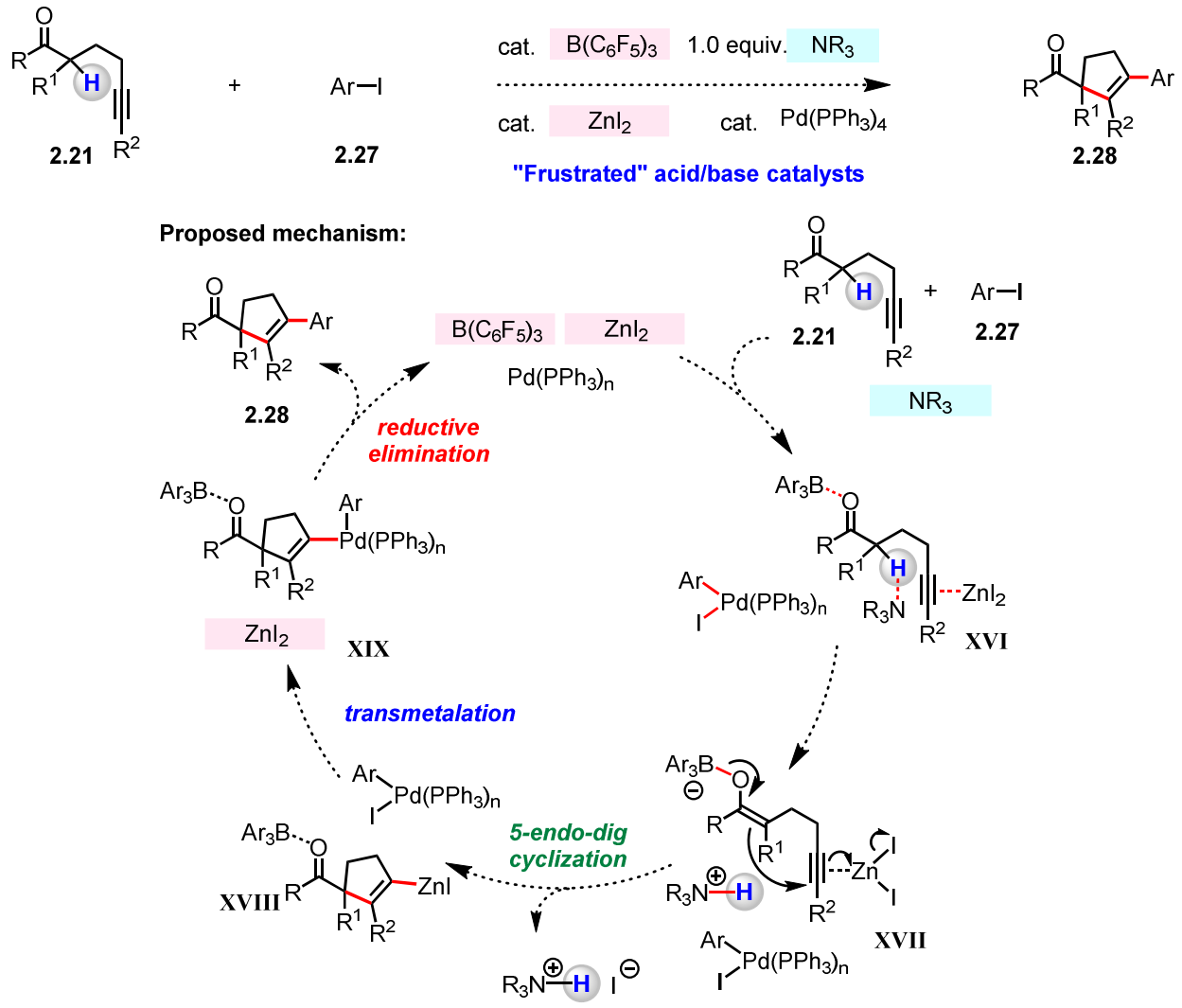
reaction conditions leads us to find that for the ester derived substrate **2.25a**, the reaction is stoichiometric with respect to the loading of ZnI_2 and PMP. The desired product can be obtained in 42% yield with 10% $B(C_6F_5)_3$, 50 mol% PMP and 50 mol% ZnI_2. Studies are underway to further enhance the applicability of this approach.

Scheme 2.15. Conia-Ene-Type Cyclization with Ester Substrate



Now we have accomplished the direct enantioselective Conia-ene-type cyclization by cooperative functions of $B(C_6F_5)_3$, *N*-alkylamine, and ZnI_2/**L** complex. However, the exact roles of ZnI_2/**L** complex, which could activate either carbonyl and/or alkyne units of **2.21**, remained undetermined. To shed light on the mechanism of the Conia-ene-type reaction, we investigated whether the proposed alkenyl ZnI intermediate **XVV** derived from **2.21** by 5-*endo-dig* carbocyclization (via **2.21** → **XVI** → **XVII** → **XVIII**; Scheme 2.16) is generated. We hypothesized that alkenyl-ZnI intermediate **XVIII** can undergo transmetallation with an appropriate Pd(II)-based complex (**XVIII** → **XIX**), which may be formed in situ through oxidative addition of $Pd(PPh_3)_4$ and an aryl iodide **2.27**. The resulting $[(Ar)(I)Pd^{II}(PPh_3)_n]$ **XIX** can then undergo C–Ar bond formation via reductive elimination to afford 1,2,3-substituted cyclopentene derivative **2.28**. The sequential Conia-ene-type carbocyclization/Negishi coupling reactions could provide evidence supporting the mechanistic hypothesis that the π-philic Zn-based catalyst is

Scheme 2.16. Sequential Conia-ene-type Cyclizations/Negishi Coupling Reaction



responsible for activation of alkyne unit in **2.21**, thereby generating **XVIII**.[15] Therefore, we need to develop a process promoted by $B(C_6F_5)_3$, *N*-alkylamine, ZnI_2, and $Pd(PPh_3)_4$ that play their

[15] For selected examples on Negishi cross coupling, see: (a) Negishi, E.; King, A. O.; Okudado, N. J. *Org. Chem.* **1977**, *42*, 1821–1823. (b) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298–3299. (c) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340–348. (d) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719–2724. (e) Zeng, X.; Quian, M.; Hu Q.; Negishi, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 2259–2263. (f) Sase, S.; Jaric, M.; Metzger, A.; Malakhov, V.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 7380–7382. (g) Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 2756–2757. (h) Han, C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 7532–7533. (i) Phapale, V. B.; Cardenas, D. J. *Chem. Soc. Rev.* **2009**, *38*, 1598–1607. (j) Haas, D.; Hammann, J. M.; Greiner, R.; Knochel, P. *ACS Catal.* **2016**, *6*, 1540–1552.

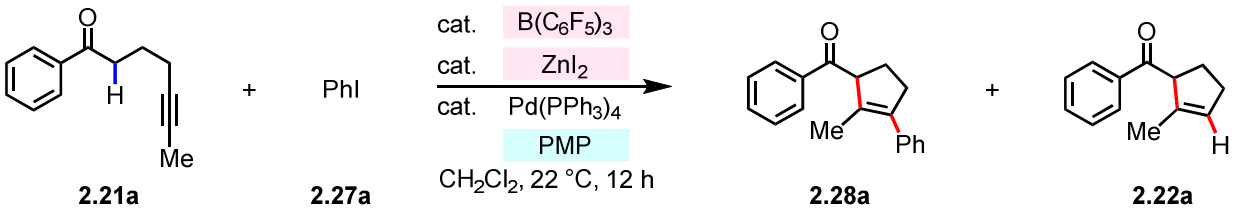
independent catalytic roles while overcoming the undesirable acid/base complexation to afford 1,2,3-substituted cyclopentenes.

For the initial investigation, we tested the ability of $B(C_6F_5)_3$, PMP, ZnI_2, and $Pd(PPh_3)_4$ to facilitate the cyclization of 1-phenylnon-5-yn-1-one **2.21a** to give the alkenyl ZnI complex **XIII**, followed by Negishi coupling with iodobenzene **2.27a** (CH_2Cl_2, 12 h, 22 °C) to generate **2.28a** (Table 2.8). With 10 mol% $B(C_6F_5)_3$, 1.0 equivalent of PMP, 50 mol% ZnI_2, and 2.0 mol% $Pd(PPh_3)_4$, desired product **2.28** can be generated in >95% yield while cyclopentene derivative **3.22a** was obtained in <5% yield (entry 1), which can be formed by protonation of alkenyl ZnI intermediate. In the absence of $Pd(PPh_3)_4$, only **2.22a** was generated in >95% yield (entry 2). Control experiments showed that when ZnI_2 or PMP was not added, neither **2.28a** nor **2.22a** were produced (entries 3–4). However, PMP, ZnI_2, and $Pd(PPh_3)_4$ were found to promote the formation of **2.28a** in 20% yield (entry 5). This observation suggests that alkynyl ketone **2.21a** can be deprotonated by cooperative functions of the Pd-based complex and PMP.[16] This reaction requires a stoichiometric amount of PMP because the formation of $[PMP–H]^+[I]^-$ (**XVII** → **XVIII**; Scheme 2.16) will inhibit the regeneration of PMP; when the loading of PMP was lowered to 50 mol%, **3.28a** was obtained in only 52% (entry 6). With 20 mol% ZnI_2, the yield of **3.22a** declined to 41% (entry 7).[17] This sequential cycloaddition/cross-coupling reaction could proceed with a minimal amount of $Pd(PPh_3)_4$ (1.0 mol%), as **3.22a** could be obtained in >95% yield (entry 8).

[16] For selected examples of transformations involving palladium enolates, see: (a) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648–2649. (b) Sodeoka, M.; Tokunoh, R.; Miyazaki, F.; Hagiwara, E.; Shibasaki, M. *Synlett* **1997**, 463–466. (c) Sodeoka, M.; Shibasaki, M. *Pure Appl. Chem.* **1998**, *70*, 411–414. (d) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474–2475. (e) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450–5458. (f) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240–11241. (g) Hayamizu, K.; Terayama, N.; Hashizume, D.; Dodo, K.; Sodeoka, M. *Tetrahedron* **2015**, *71*, 6594–6601.

[17] (a) Kálmán, E.; Serke, I.; Pálinkás, G.; Johansson, G.; Kabisch, G.; Maeda, M.; Ohtaki, H. *Z. Naturforsch. A*. **1983**, *38*, 225–230. (b) Wakita, H.; Johansson, G.; Sandström, M.; Goggin, P. L.; Ohtaki, H. *J. Solution Chem.* **1991**, *20*, 643–668. (c) Maeda, M.; Ito, T.; Hori, M.; Johansson, G. *Z. Naturforsch. A*. **1996**, *51*, 63–70.

Table 2.8. Evaluation of Reaction Parameters for Sequential Conia-ene-type Cyclizations/Negishi Coupling Reaction [a,b]



2.21a **2.27a** **2.28a** **2.22a**

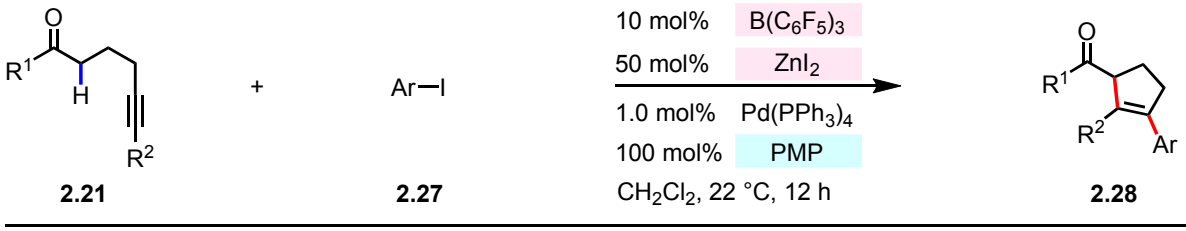
entry	$B(C_6F_5)_3$ (mol%)	PMP (mol%)	ZnI_2 (mol%)	$Pd(PPh_3)_4$ (mol%)	yield(%) **2.28a**	yield(%) **2.22a**
1	10	100	50	2	>95	<5
2	10	100	50	none	0	>95
3	10	100	none	2	0	0
4	10	none	50	2	0	0
5	none	100	50	2	20	0
6	10	50	50	2	52	<5
7	10	100	20	2	41	<5
8	10	100	50	1	>95	<5

[a] Conditions: 1-phenylnon-5-yn-1-one (**2.21a**, 0.10 mmol), iodobenzene (**2.27a**, 0.12 mmol), $B(C_6F_5)_3$, PMP, ZnI_2, $Pd(PPh_3)_4$, CH_2Cl_2 (0.5 mL), under N_2, 22 °C, 12 h. [b] Yield was determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard.

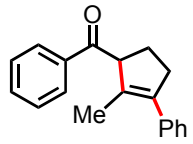
Various alkynyl ketones and aryl- and heteroaryl-iodides proved to be suitable substrates for the sequential Conia-ene-type carbocyclization/Negishi coupling (**2.28a**–**2.28l**; Table 2.9). Phenyl, naphthalen-2-yl, 2-methoxyphenyl, and furan-2-yl-substituted ketones gave the corresponding products (**2.28a**–**2.28e**) in 65 to 98% yield. An alkyl substituted ketone was also found to be a suitable substrate as **2.28f** was obtained in 91% yield. Cyclopentene derivatives with 1-naphthyl group (**2.28g**) as well as those containing arenes with electron-donating (**2.28h**) and electron-withdrawing (**2.28i**–**2.28k**) groups were obtained in 91 to 95% yield. Heteroaryl substituted **2.28l** could also be produced in 85% yield. Here, we have developed a cooperative

catalyst system which constitutes of $B(C_6F_5)_3$, an amine, ZnI_2, and $Pd(PPh_3)_4$ to promote sequential Conia-ene-type cycloaddition/Negishi coupling reactions. Furthermore, the results provide a mechanistic insight into that π-philic Zn-based catalyst is responsible for activation of alkyne unit in **2.21**, while $B(C_6F_5)_3$ would activate the carbonyl units.

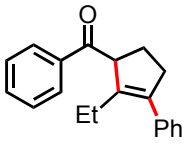
Table 2.9. Sequential Conia-ene-type Cyclizations/Negishi Coupling Reaction with Different Ketones [a,b]



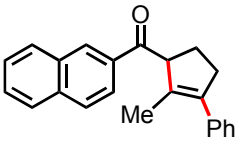
2.21 **2.27** **2.28**



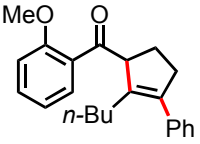
2.28a, 95% yield



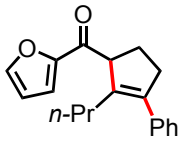
2.28b, 98% yield



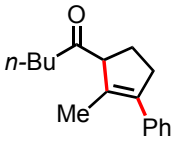
2.28c, 91% yield



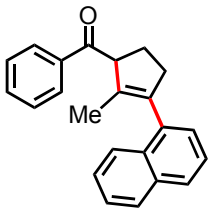
2.28d, 75% yield



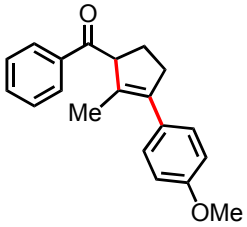
2.28e, 65% yield



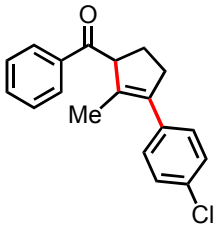
2.28f, 91% yield



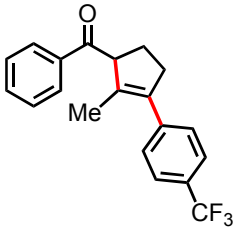
2.28g, 92% yield



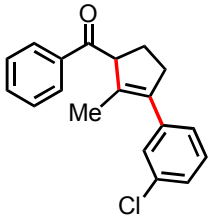
2.28h, 95% yield



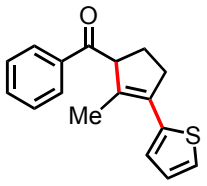
2.28i, 93% yield



2.28j, 91% yield



2.28k, 92% yield



2.28l, 85% yield

[a] Conditions: Alkynl ketone (**2.21**, 0.10 mmol), aryl iodide (**2.27**, 0.12 mmol), $B(C_6F_5)_3$ (10 mol%), PMP (100 mol%), ZnI_2 (50 mol%), $Pd(PPh_3)_4$ (1.0 mol%), CH_2Cl_2 (0.5 mL), under N_2, 22 °C, 12 h. [b] Yield of isolated and purified product.

2.5. Conclusions and Future Outlook

In summary, we have developed the direct catalytic enantioselective Conia-ene-type reaction with mono-carbonyl compound by implementing the cooperative functions of a three-component catalyst system, which consists of a pair of Lewis acids and a Brønsted basic amine. Furthermore, through incorporating $Pd(PPh_3)_4$ co-catalyst, the sequential Conia-ene-type cycloaddition/Negishi coupling reactions can be accomplished. These two reactions have clearly demonstrated that a combination of multiple different catalyst units can work cooperatively to promote the union of in situ generated reactive intermediates from poorly acid- and base-sensitive starting materials. The principles outlined herein, entailing separate and independently operational catalysts, provide a rational framework for the development of novel enantioselective cooperative catalyst systems to produce synthetically and biologically important compounds.

2.6. Expeirimental

2.6.1 Procedures, Materials and Instrumentation

General Experimental Procedures. All reactions were performed in standard, oven-dried glassware fitted with rubber septa under an inert atmosphere of nitrogen unless otherwise described. Stainless steel syringes or cannulas were used to transfer air- and moisture-sensitive liquids. Reported concentrations refer to solution volumes at room temperature. Evaporation and concentration *in vacuo* were performed using house vacuum (ca. 40 mm Hg). Column chromatography was performed with SiliaFlash® 60 (40–63 micron) silica gel from Silicycle. Thin layer chromatography (TLC) was used for reaction monitoring and product detection using pre-coated glass plates covered with 0.25 mm silica gel with fluorescent indicator; visualization by UV light (λ_{ex} = 254 nm) or $KMnO_4$ stain.

Materials. Reagents were purchased in reagent grade from commercial suppliers and used without further purification, unless otherwise described. H_2O, in synthetic procedures, refers to distilled water. Chiral ligands **L1**-**L12** were prepared according to the procedures previously reported in the literature.[13-14,18-19] Substrates **2.21**, **2.23a,** and **2.25a** were also synthesized according to the literature procedures.[20]

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[18] Tse, M. D.; Bhor, S.; Klawonn, M.; Anilkumar, G.; Jiao, H.; Döbler, C.; Spannenberg, A.; Mägerlein, W.; Hugl, H.; Beller, M. *Chem. Eur. J.* **2006**, *12*, 1855–1874.

[19] Itoh, K.; Sibi, M. P. *Org. Biomol. Chem.* **2018**, *16*, 5551–5565.

[20] (a) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2006**, *128*, 6499–6507. (b) Wang, L.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2018**, *57*, 6910–6914. (c) Chen, W.; Ma, L.; Paul, A.; Seidel, D. *Nat. Chem.* **2018**, *10*, 165–169. (d) Ramachary, D. B.; Kishor, M. *J. Org. Chem.* **2007**, *72*, 5056–5068. (e) Zhao, Y. S.; Tang, X. Q.; Tao, J. C.; Tian, P.; Lin, G. Q. *Org. Biomol. Chem.* **2016**, *14*, 4400–4404. (f) Wu, X.; Chen, Z.; Bai, Y. B.; Dong, V. M. *J. Am. Chem. Soc.* **2016**, *138*, 12013–12016. (g) Wu, Y.; Arenas, I.; Broomfield, L. M.; Martin, E.; Shafir, A. *Chem. Eur. J.* **2015**, *21*, 18779–18784. (h) Meiß, R.; Kumar, K.; Waldmann, H. *Chem. Eur. J.* **2015**, *21*, 13526–13530. (i) Miesch; L.; Welsch, T.; Rietsch, V.; Miesch, M. *Chem. Eur. J.* **2009**, *15*, 4394–4401. (j) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328–6335.

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra and proton-decoupled carbon nuclear magnetic resonance (^{13}C {^{1}H} NMR) spectra were recorded at 25°C (unless stated otherwise) on Inova 600 (600 MHz) or Varian Unity/Inova 500 (500 MHz) or Oxford AS400 (400 MHz) spectrometers at the Boston College nuclear magnetic resonance facility. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent. Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent. The solvent peak was referenced to 0 ppm for ^{1}H for tetramethylsilane and 77.0 ppm for ^{13}C for $CDCl_3$. Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sp = septet, m = multiplet), coupling constants in Hertz (Hz).

Optical rotations were measured using a 1 mL cell with a 5 cm path length on a Rudolph Research Analytical Autopol IV Polarimeter. Infrared spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer. Data are represented as follows: frequency of absorption (cm^{-1}). High-resolution mass spectrometry was performed on a JEOL AccuTOF-DART (positive mode) or Agilent 6220 TOF-ESI (positive mode) at the Mass Spectrometry Facility, Boston College. Chiral HPLC analyses were carried using Agilent 1200 series instruments with Daicel CHIRALPAK® columns or Daicel CHIRALCEL® columns (internal diameter 4.6 mm, column length 250 mm, particle size 5 μm).

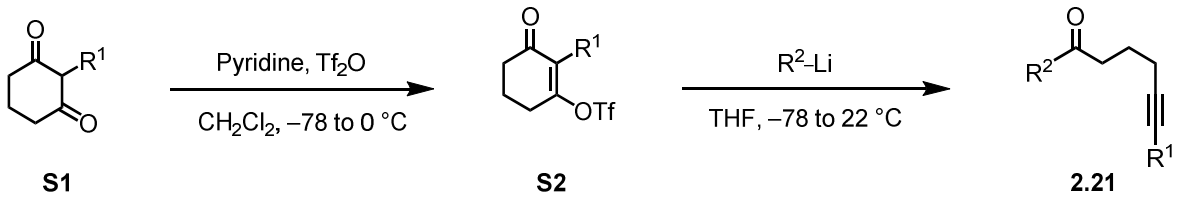
Abbreviations Used. Bn = benzyl, DART = direct analysis in real time, DCE = 1,2-ichloroethane, DCM = dichloromethane, er = enantiomeric ratio, Et_2O = diethyl ether, EtOAc = ethyl acetate, H_2O = water, HPLC = high pressure liquid chromatography, HR = high-resolution, LC = liquid chromatography, MS = mass spectrometry, NA = not applicable, PMP = 1,2,2,6,6-pentamethylpiperidine, PTFE = Polytetrafluoroethylene, PTLC = preparative thin layer

chromatography, Tf = trifluromethanesulfonate, THF = tetrahydrofuran, TOF = time-of-flight, Ts = 4-toluenesulfonyl.

2.6.2 Experimental Section

2.6.2.1 Substrate Preparation

General Procedure A:



S1 **S2** **2.21**

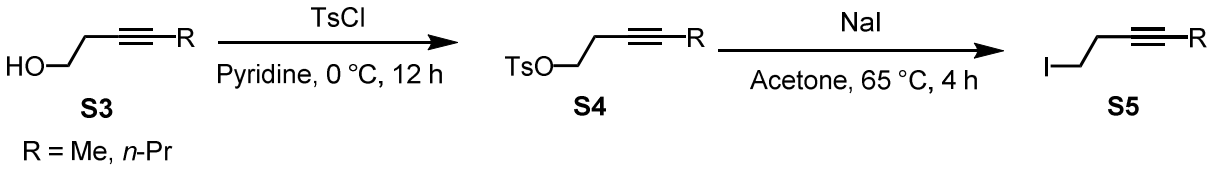
Preparation of S2:

To a solution of cyclohexanedione **S1** (1.0 equiv.) in dichloromethane (0.2 M), pyridine (2.0 equiv.) was added. The mixture was then cooled to –78 °C and trifluoromethane sulfonic anhydride (Tf_2O, 1.2 equiv.) was added slowly at –78 °C. The reaction mixture was allowed to stir for 10 min at –78 °C and warmed to 0 °C. After the starting material (**S1**) was consumed (as determined by TLC), the mixture was acidified with 1N HCl (aq.) and extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (pentane:ether = 5:1) to yield **S2**.[20a]

Preparation of 2.21:

To a solution of **S2** (1.0 equiv.) in THF (0.25 M) at −78 °C under N_2 atmosphere was added R^2–Li (0.9 equiv.),[20b-20c] dropwise. The reaction mixture was allowed to stir at −78 °C for 10 minutes, then for 10 minutes at 0 °C, followed by 30 minutes at room temperature. Upon completion of the reaction, saturated NH_4Cl (aq.) was added to quench the reaction and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting mixture was purified by silica gel column chromatography using (hexanes:ethyl acetate = 100:1) to afford **2.21**.[20a]

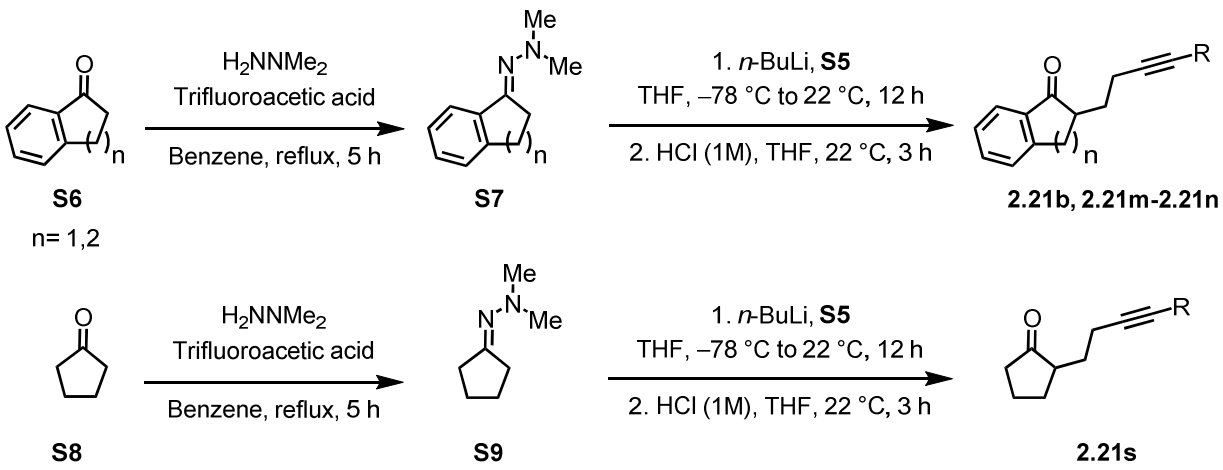
General Procedure B:



R = Me, *n*-Pr

Synthesis of S5:

S5 was prepared from **S3** according to the known procedures.[20h] To a solution of the alkynol **S3** (1.0 equiv.) in dry pyridine (1.25 M) was added *p*-toluene sulfonyl chloride (1.1 equiv.) and the reaction mixture was allowed to stir at 0 °C for 12 h. Upon completion, the reaction mixture was poured into water and was subsequently extracted with Et_2O (3 x 50 mL). The combined ether layers were washed with saturated $CuSO_4$ (aq.) and brine, and then dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*, and the crude product **S4** was used without further purification. To a solution of **S4** (1.0 equiv.) in acetone (0.4 M) was added sodium iodide (3.0 equiv.). The reaction mixture was allowed to heat at reflux for 4 h. Subsequently, the reaction mixture was concentrated *in vacuo*, and the resulting mixture was poured into water and extracted with pentane (3 x 50 mL). The combined organic layers were washed with water then brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting mixture was purified by silica gel column chromatography (hexanes:ethyl acetate = 50:1) to afford **S5** as a colorless liquid.



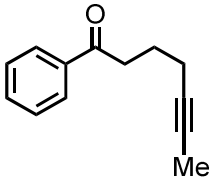
Synthesis of S7 and S9:

To a stirred solution of cycloketone **S6** or **S8** (1.0 equiv.) in benzene (0.6 M) was added *N*,*N*-dimethylhydrazine (1.2 equiv.) and trifluoroacetic acid (10 drops). The mixture was allowed to stir at reflux for 15 h with a Dean-Stark apparatus. Benzene was removed by distillation at atmospheric pressure. The residue was dissolved in Et_2O (30 mL), and ice water (25 mL) was added. After extraction with Et_2O (3 x 20 mL), the combined organic layers were washed with brine and dried over Na_2SO_4. After filtration and removal of the solvent, the residue was purified by distillation to give the desired compound **S7** or **S9**.[20i]

Synthesis of 1l-1n, 1s:

To a solution of *N*,*N*-dimethylhydrazone **S7** or **S9** (1.0 equiv.) in THF (0.25 M) was added *n*-BuLi (1.2 equiv.), dropwise at −5 °C. The reaction mixture was allowed to stir for 1 h at −5 °C, whereupon a solution of **S5** (1.1 equiv.) in THF (1 M) was added dropwise. The reaction mixture was allowed to stir at room temperature for 12 h, then 2N HCl (aq., 20 mL) was added to the solution. The reaction mixture was allowed to stir at room temperature for 3 h and extracted with ethyl acetate (5 x 10 mL). The combined organic layers were successively washed with aqueous $Na_2S_2O_4$ solution (2 x 50 mL), brine (2 x 50 mL) and dried over Na_2SO_4. After filtration and

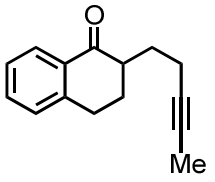
removal of the solvent, the residue was purified by silica gel column chromatography to give compound **2.21**.[20i]



2.21a

1-Phenylhept-5-yn-1-one (2.21a)

1-Phenylhept-5-yn-1-one was prepared following the **General Procedure A** starting with 10 mmol of 2-methylcyclohexane-1,3-dione. The product was obtained as a colorless oil (1.7 g, 90% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 9.7 Hz, 2H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.49 – 7.44 (m, 2H), 3.10 (t, *J* = 7.3 Hz, 2H), 2.31 – 2.23 (m, 2H), 1.92 (p, *J* = 7.0 Hz, 2H), 1.78 (t, *J* = 2.6 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.50, 139.67, 135.59, 131.19, 130.68, 81.04, 79.06, 39.98, 26.06, 20.93, 6.11; **IR** (neat) 2934, 2915, 1681, 1595, 1579, 1446, 1365, 1319, 1228, 1198, 1000, 745, 689 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{13}H_{15}O$ (MH^+): 187.11174; found: 187.11099.

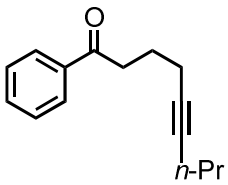


2.21b

2-(Pent-3-yn-1-yl)-3,4-dihydronaphthalen-1(2*H*)-one (2.21b)

2-(Pent-3-yn-1-yl)-3,4-dihydronaphthalen-1(2*H*)-one was prepared following the **General Procedure B** starting with 20 mmol of 3,4 dihydronaphthalen-1(2*H*)-one. The product was obtained as a brown oil (2.8 g, 67% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 3.10 – 2.96 (m, 2H), 2.70 – 2.62 (m, 1H), 2.44 – 2.32 (m, 1H), 2.32 – 2.16 (m, 3H), 1.93 – 1.82 (m, 1H), 1.76 (s, 3H), 1.67 – 1.54 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.65, 146.51, 135.77, 135.21, 131.30,

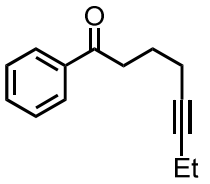
130.04, 129.19, 81.13, 78.85, 48.97, 31.61, 31.26, 30.93, 19.15, 6.13; **IR** (neat) 2915, 2856, 1678, 1598, 1452, 1226, 891, 739 cm^{-1}; **HRMS** (DART) Calcd for $C_{15}H_{15}O$ (MH^+): 213.12739; found: 213.12708.



2.21c

1-Phenylnon-5-yn-1-one (2.21c)

1-Phenylnon-5-yn-1-one was prepared following the **General Procedure A** starting with 30 mmol of 2-propylcyclohexane-1,3-dione.[20d] The product was obtained as a pale-yellow oil (5.9 g, 92% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 9.5 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 3.11 (t, *J* = 7.3 Hz, 2H), 2.33 – 2.26 (m, 2H), 2.17 – 2.09 (m, 2H), 1.93 (p, *J* = 7.0 Hz, 2H), 1.50 (h, *J* = 7.3 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.55, 139.68, 135.59, 131.19, 130.69, 83.78, 81.99, 39.97, 26.20, 25.12, 23.40, 20.97, 16.13; **IR** (neat) 2958, 2930, 2869, 1682, 1596, 1579, 1447, 1366, 1228, 1000, 745, 689 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{15}H_{19}O$ (MH^+): 215.1430; found: 215.14261.

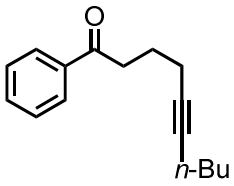


2.21d

1-Phenyloct-5-yn-1-one (2.21d)

1-Phenyloct-5-yn-1-one was prepared following the **General Procedure A** starting with 10 mmol of 2-ethylcyclohexane-1,3-dione.[20d] The product was obtained as a yellow oil (1.7 g, 88% yield).

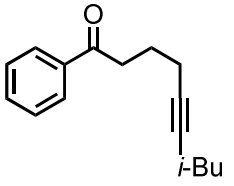
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.1 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 3.11 (t, *J* = 7.3 Hz, 2H), 2.29 (t, *J* = 6.7 Hz, 2H), 2.16 (q, *J* = 7.1 Hz, 2H), 1.93 (p, *J* = 7.1 Hz, 2H), 1.11 (t, *J* = 7.9 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.54, 139.68, 135.59, 131.19, 130.69, 85.31, 81.20, 39.95, 26.16, 20.94, 16.96, 15.05; **IR** (neat) 2970, 2934, 1681, 1596, 1579, 1447, 1366, 1318, 1228, 1000, 745, 689 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{14}H_{17}O$ (MH^+): 201.12739; found: 201.12675.



2.21e

1-Phenyldec-5-yn-1-one (2.21e)

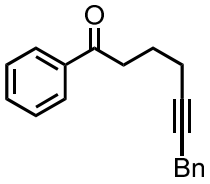
1-Phenyldec-5-yn-1-one was prepared following the **General Procedure A** starting with 10 mmol of 2-butylylcyclohexane-1,3-dione.[20d] The product was obtained as a colorless oil (1.9 g, 85% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.1 Hz, 2H), 7.56 (t, 1H), 7.47 (t, *J* = 7.9 Hz, 2H), 3.11 (t, *J* = 7.3 Hz, 2H), 2.33 – 2.26 (m, 2H), 2.19 – 2.11 (m, 2H), 1.97 – 1.87 (m, 2H), 1.50 – 1.33 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.55, 139.68, 135.58, 131.19, 130.69, 83.92, 81.81, 39.96, 33.82, 26.18, 24.59, 21.07, 20.97, 16.26; **IR** (neat) 2953, 2929, 1683, 1596, 1447, 1366, 1228, 1000, 743, 689 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{16}H_{21}O$ (MH^+): 229.15869; found: 229.15855.



2.21f

8-Methyl-1-phenylnon-5-yn-1-one (2.21f)

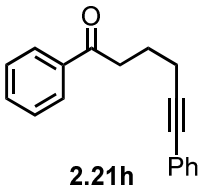
8-Methyl-1-phenylnon-5-yn-1-one was prepared following the **General Procedure A** starting with 10 mmol of 2-isobutylcyclohexane-1,3-dione.[20e] The product was obtained as a colorless oil (1.8 g, 78% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.5 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 3.12 (t, *J* = 7.3 Hz, 2H), 2.33 – 2.28 (m, 2H), 2.07 – 2.02 (m, 2H), 1.94 (p, *J* = 7.0 Hz, 2H), 1.81 – 1.71 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.54, 139.67, 135.59, 131.19, 130.68, 82.79, 82.71, 39.99, 30.87, 30.63, 26.24, 24.60, 20.99; **IR** (neat) 2953, 2903, 1683, 1595, 1579, 1447, 1366, 1228, 1000, 748, 689 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{16}H_{21}O$ (MH^+): 229.15869; found: 229.15854.



2.21g

1,7-Diphenylhept-5-yn-1-one (2.21g)

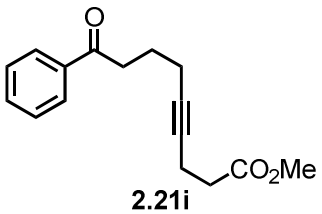
1,7-Diphenylhept-5-yn-1-one was prepared following the **General Procedure A** starting with 10 mmol of 2-benzylcyclohexane-1,3-dione.[20d] The product was obtained as a yellow oil (2.4 g, 90% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 9.6 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.36 – 7.27 (m, 4H), 7.22 (t, *J* = 7.2 Hz, 1H), 3.58 (s, 2H), 3.13 (t, *J* = 7.3 Hz, 2H), 2.40 – 2.33 (m, 2H), 1.98 (p, *J* = 7.0 Hz, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.45, 140.14, 139.68, 135.65, 131.25, 131.14, 130.73, 130.53, 129.14, 84.38, 81.43, 39.96, 27.85, 26.07, 21.08; **IR** (neat) 3057, 3019, 1679, 1595, 1156, 1000, 728, 688 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{19}H_{19}O$ (MH^+): 263.14304; found: 263.14192.



2.21h

1,6-Diphenylhex-5-yn-1-one (2.21h)

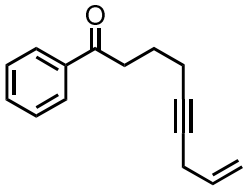
1,6-Diphenylhex-5-yn-1-one was prepared based on a known procedure with the following modifications.[20j] To a solution of iodobenzene (4.3 g, 21 mmol, 2.1 equiv.), 1-phenylhex-5-yn-1-one[20a] (1.7 g, 10 mmol, 1.0 equiv.), triethylamine (20.2 g, 200 mmol, 20 equiv.) in THF (2 M) under N_2 was added $Pd(PPh_3)_4$ (115 mg, 0.1 mmol, 1 mol%) and CuI (38 mg, 0.2 mmol, 2 mol%). The reaction mixture was allowed to stir at 22 °C for 12 h. The mixture was filtered through a plug of Celite and the filtrate was washed with Et_2O, then concentrated under reduced pressure. The product was purified by column chromatography (hexanes:ethyl acetate = 20:1) to give the desired product as pale-yellow oil (2.4 g, 95% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.1 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.38 (dd, *J* = 6.5, 3.2 Hz, 2H), 7.31 – 7.26 (m, 3H), 3.19 (t, *J* = 7.2 Hz, 2H), 2.56 (t, *J* = 6.8 Hz, 2H), 2.06 (p, *J* = 7.0 Hz, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.37, 139.63, 135.68, 134.21, 131.25, 130.87, 130.71, 130.31, 126.43, 91.96, 84.13, 39.92, 25.81, 21.61; **IR** (neat) 3055, 2934, 1681, 1595, 1488, 1446, 1228, 755, 689 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{18}H_{17}O$ (MH^+): 249.12739; found: 249.12754.



2.21i

Methyl 9-oxo-9-phenylnon-4-ynoate (2.21i)

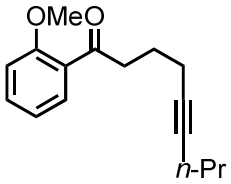
Methyl 9-oxo-9-phenylnon-4-ynoate was prepared following the **General Procedure A** starting with 10 mmol of methyl 3-(2,6-dioxocyclohexyl) propanoate.[20f] The product was obtained as a colorless oil (1.7 g, 65% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 9.6 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 3.66 (s, 3H), 3.09 (t, *J* = 7.3 Hz, 2H), 2.52 – 2.44 (m, 4H), 2.30 – 2.25 (m, 2H), 1.91 (p, *J* = 7.0 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 199.80, 172.51, 136.99, 132.96, 128.55, 128.03, 80.17, 79.09, 51.65, 37.19, 33.79, 23.27, 18.22, 14.74; **IR** (neat) 2948, 1735, 1682, 1446, 1365, 1229, 1165, 749, 650 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{16}H_{19}O_3$ (MH^+): 259.1329; found: 259.13287.



2.21j

1-Phenylnon-8-en-5-yn-1-one (2.21j)

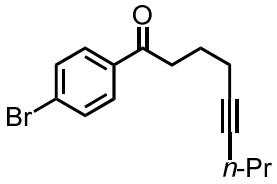
1-Phenylnon-8-en-5-yn-1-one was prepared following the **General Procedure A** starting with 10 mmol of 2-allylcyclohexane-1,3-dione.[20g] The product was obtained as a colorless oil (1.8 g, 87% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 5.87 – 5.77 (m, 1H), 5.30 (dd, *J* = 16.9, 1.8 Hz, 1H), 5.09 (dd, *J* = 9.9, 1.7 Hz, 1H), 3.12 (t, *J* = 7.3 Hz, 2H), 2.97 – 2.91 (m, 2H), 2.38 – 2.30 (m, 2H), 1.96 (p, *J* = 7.0 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 200.12, 137.34, 133.57, 133.29, 128.89, 128.37, 116.00, 82.17, 77.94, 37.63, 23.76, 23.45, 18.68; **IR** (neat) 2935, 2896, 1682, 1596, 1447, 1367, 1199, 990, 914, 750, 689 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{15}H_{17}O$ (MH^+): 213.12739; found: 213.12681.



2.21k

1-(2-Methoxyphenyl)non-5-yn-1-one (2.21k)

1-(2-Methoxyphenyl)non-5-yn-1-one was prepared following the **General Procedure A** starting with 10 mmol of 2-propylcyclohexane-1,3-dione.[20d] The product was obtained as a colorless oil (1.7 g, 72% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.48 – 7.42 (m, 1H), 7.03 – 6.94 (m, 2H), 3.90 (s, 3H), 3.09 (t, *J* = 7.3 Hz, 2H), 2.28 – 2.22 (m, 2H), 2.16 – 2.08 (m, 2H), 1.91 – 1.84 (m, 2H), 1.49 (h, *J* = 7.2 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.37, 158.44, 133.19, 130.17, 128.58, 120.59, 111.50, 80.66, 79.67, 55.44, 42.69, 23.81, 22.48, 20.76, 18.43, 13.45; **IR** (neat) 2958, 2931, 1671, 1595, 1483, 1462, 1435, 1282, 1243, 1023, 756 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{16}H_{21}O_2$ (MH^+): 245.15361; found: 245.15500.

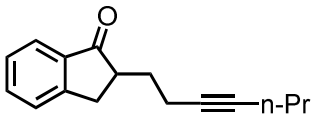


2.21l

1-(4-Bromophenyl)non-5-yn-1-one (2.21l)

1-(4-Bromophenyl)non-5-yn-1-one was prepared following the **General Procedure A** starting with 10 mmol of 2-propylcyclohexane-1,3-dione.[20d] The product was obtained as a colorless oil (2.2 g, 76% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 3.07 (t, *J* = 7.3 Hz, 2H), 2.32 – 2.26 (m, 2H), 2.15 – 2.09 (m, 2H), 1.92 (p, *J* = 7.0 Hz, 2H), 1.50 (q, *J* = 7.2 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 198.80, 135.72,

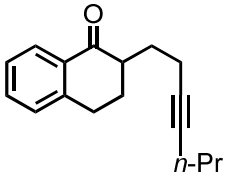
131.84, 129.57, 128.07, 81.25, 79.18, 37.23, 23.41, 22.46, 20.73, 18.25, 13.48; **IR** (neat) 2957, 2930, 1683, 1583, 1394, 1227, 1068, 1009, 991, 809 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{15}H_{18}OBr$ (MH^+): 293.05355; found: 293.05285.



2.21m

2-(Hept-3-yn-1-yl)-2,3-dihydro-1*H*-inden-1-one (2.21m)

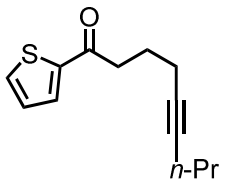
2-(Hept-3-yn-1-yl)-2,3-dihydro-1*H*-inden-1-one was prepared following the **General Procedure B** starting with 20 mmol of 2,3-dihydro-1*H*-inden-1-one. The product was obtained as a dark brown oil (2.2 g, 50% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 3.43 – 3.33 (m, 1H), 2.91 – 2.81 (m, 2H), 2.48 – 2.31 (m, 2H), 2.25 – 2.14 (m, 1H), 2.14 – 2.06 (m, 2H), 1.69 – 1.60 (m, 1H), 1.49 (dt, *J* = 14.5, 7.2 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 211.14, 156.17, 139.42, 137.31, 130.01, 129.16, 126.52, 83.94, 81.71, 49.24, 35.35, 33.36, 25.06, 23.39, 19.79, 16.14; **IR** (neat) 2957, 2927, 1708, 1607, 1462, 1275, 747 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{16}H_{19}O$ (MH^+): 227.14304; found: 227.14176.



2.21n

2-(Hept-3-yn-1-yl)-3,4-dihydronaphthalen-1(2*H*)-one (2.21n)

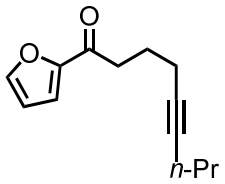
2-(Hept-3-yn-1-yl)-3,4-dihydronaphthalen-1(2*H*)-one was prepared following the **General Procedure B** starting with 20 mmol of 3,4-dihydronaphthalen-1(2*H*)-one. The product was obtained as a brown oil (3.0 g, 62% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.9 Hz, 1H), 7.50 – 7.42 (m, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 1H), 3.07 – 2.99 (m, 2H), 2.73 – 2.63 (m, 1H), 2.44 – 2.36 (m, 1H), 2.36 – 2.20 (m, 3H), 2.15 – 2.08 (m, 2H), 1.93 – 1.83 (m, 1H), 1.68 – 1.57 (m, 1H), 1.49 (h, *J* = 7.3 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.65, 146.53, 135.76, 135.21, 131.30, 130.05, 129.20, 83.54, 82.07, 49.05, 31.64, 31.30, 30.90, 25.12, 23.41, 19.20, 16.13; **IR** (neat) 2956, 2927, 2863, 2837, 1679, 1598, 1453, 1432, 1226, 909, 773 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{17}H_{21}O$ (MH^+): 241.15869; found: 241.15897.



2.21o

1-(Thiophen-2-yl)non-5-yn-1-one (2.21o)

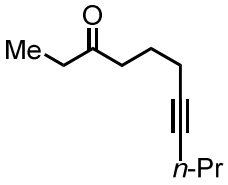
1-(Thiophen-2-yl)non-5-yn-1-one was prepared following the **General Procedure A** starting with 10 mmol of 2-propylcyclohexane-1,3-dione.[20d] The product was obtained as a pale-yellow oil (1.8 g, 82% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 4.8 Hz, 1H), 7.63 (d, *J* = 6.0 Hz, 1H), 7.15 – 7.12 (m, 1H), 3.04 (t, *J* = 7.3 Hz, 2H), 2.29 (tt, *J* = 6.8, 2.4 Hz, 2H), 2.13 (tt, *J* = 7.1, 2.4 Hz, 2H), 1.93 (p, *J* = 7.0 Hz, 2H), 1.50 (h, *J* = 7.3 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 195.44, 147.04, 136.04, 134.41, 130.69, 83.83, 81.84, 40.63, 26.50, 25.09, 23.36, 20.93, 16.11; **IR** (neat) 2957, 2930, 1657, 1516, 1412, 1336, 1234, 1067, 718 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{13}H_{17}OS$ (MH^+): 221.09946; found: 221.10027.



2.21p

1-(Furan-2-yl)non-5-yn-1-one (2.21p)

1-(Furan-2-yl)non-5-yn-1-one was prepared following the **General Procedure A** starting with 10 mmol of 2-propylcyclohexane-1,3-dione.[20d] The product was obtained as a pale-yellow oil (1.6 g, 79% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 0.9 Hz, 1H), 7.20 (d, *J* = 4.2 Hz, 1H), 6.53 (dd, *J* = 3.5, 1.7 Hz, 1H), 2.95 (t, *J* = 7.4 Hz, 2H), 2.30 – 2.24 (m, 2H), 2.16 – 2.08 (m, 2H), 1.95 – 1.87 (m, 2H), 1.50 (q, *J* = 7.2 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 191.72, 155.41, 148.87, 119.53, 114.74, 83.79, 81.82, 39.86, 26.11, 25.08, 23.36, 20.97, 16.09; **IR** (neat) 2959, 2931, 1675, 1567, 1467, 1393, 1224, 1013, 812, 761 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{13}H_{17}O_2$ (MH^+): 205.1223; found: 205.12050.

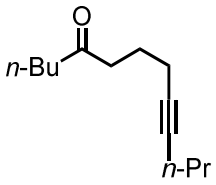


2.21q

Undec-7-yn-3-one (1q)

Undec-7-yn-3-one was prepared following the **General Procedure A** starting with 10 mmol of 2-propylcyclohexane-1,3-dione.[20d] The product was obtained as a colorless oil (1.0 g, 60% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.53 (t, *J* = 6.7 Hz, 2H), 2.44 (qd, *J* = 7.3, 1.3 Hz, 2H), 2.19 (t, *J* = 6.8 Hz, 2H), 2.12 (t, *J* = 7.6 Hz, 2H), 1.76 (p, *J* = 7.1 Hz, 2H), 1.50 (h, *J* = 7.3 Hz, 2H), 1.06 (t, *J* = 7.6 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 214.03, 83.79, 82.07,

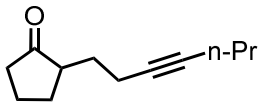
43.81, 38.86, 25.94, 25.33, 23.57, 21.04, 16.30, 10.66; **IR** (neat) 2958, 2932, 1711, 1456, 1373, 1112 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{11}H_{19}O$ (MH^+): 167.14304; found: 167.14235.



2.21r

Tridec-9-yn-5-one (2.21r)

Tridec-9-yn-5-one was prepared following the **General Procedure A** starting with 10 mmol of 2-propylcyclohexane-1,3-dione.[20d] The product was obtained as a colorless oil (1.40g, 72% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.53 (t, *J* = 7.3 Hz, 2H), 2.41 (t, *J* = 7.5 Hz, 2H), 2.23 – 2.16 (m, 2H), 2.16 – 2.10 (m, 2H), 1.75 (p, *J* = 7.1 Hz, 2H), 1.62 – 1.45 (m, 4H), 1.36 – 1.27 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 213.59, 83.58, 81.87, 45.31, 43.96, 28.63, 25.65, 25.11, 24.98, 23.35, 20.80, 16.47, 16.09; **IR** (neat) 2956, 2930, 2869, 1711, 1454, 1370, 1125, 1083 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{13}H_{23}O$ (MH^+): 195.17434; found: 195.17324.



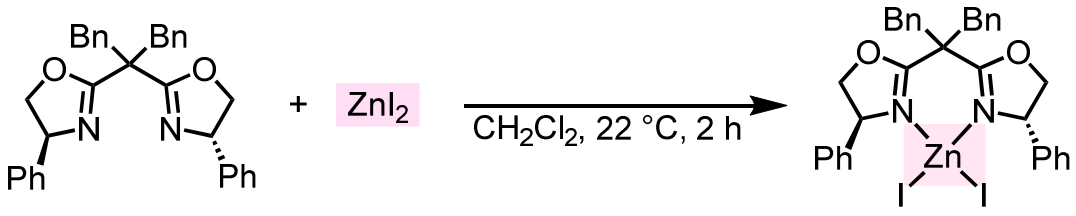
2.21s

2-(Hept-3-yn-1-yl)cyclopentan-1-one (2.21s)

2-(Hept-3-yn-1-yl)cyclopentan-1-one was prepared following the **General Procedure B** starting with 20 mmol of cyclopentanone**.** The product was obtained as a brown oil (2.8 g, 78% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.37–2.17 (m, 5H), 2.17 – 2.07 (m, 3H), 2.07 – 1.91 (m, 2H), 1.79 (d, *J* = 9.0 Hz, 1H), 1.58 – 1.38 (m, 4H), 0.96 (t, *J* = 7.8 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ

223.66, 83.51, 81.83, 50.87, 40.73, 32.06, 31.77, 25.08, 23.37, 23.35, 19.67, 16.10; **IR** (neat) 2958, 2930, 2868, 1734, 1452, 1153 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{12}H_{19}O$ (MH^+): 179.14304; found: 179.14191.

2.6.2.2 Preparation Chiral ZnI_2/BOX Complexes



L10 ZnI_2/**L10**

Chiral ZnI_2/BOX complex (ZnI_2/**L10**) was prepared according to a literature procedure.[15,21] To a 25 mL oven-dried sealed tube was added (4*S*,4'*S*)-2,2'-(1,3-diphenylpropane-2,2-diyl)bis(4-phenyl-4,5-dihydrooxazole) (**L10**, 973 mg, 2.0 mmol), ZnI_2 (766 mg, 2.4 mmol), and CH_2Cl_2 (10 mL) under nitrogen atmosphere. The resulting mixture was allowed to stir at 22 °C for 2 h. Upon completion, the solution was transferred to a syringe fitted with a 0.22 μm PTFE filter and filtered under nitrogen into a Schlenk tube. The solvent was removed *in vacuo* to deliver **ZnI_2/L10** complex as a pale yellow solid (1.5 g, 95% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.42 (m, 6H), 7.28 – 7.21 (m, 2H), 7.21 – 7.11 (m, 8H), 6.62 (d, *J* = 7.5 Hz, 4H), 5.69 (t, *J* = 10.5 Hz, 2H), 4.96 (t, *J* = 9.8 Hz, 2H), 4.22 (t, *J* = 9.7 Hz, 2H), 3.91 (d, *J* = 14.2 Hz, 2H), 3.44 (d, *J* = 14.2 Hz, 2H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.43, 135.45, 133.74, 130.04, 129.21, 128.95, 128.88, 128.39, 128.24, 75.40, 68.43, 51.85, 44.63.

[21] Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D.M.; Campos, K.R.; Woerpel, K.A. *J. Org. Chem.* **1998**, *63*, 4541–4544.

2.6.2.3 Experimental Procedure for Optimization Studies

Experimental Procedure for Optimization of Racemic Conia-Ene-Type Reaction (see Tables 2.1 and Tables 2.2)

To a 7.0 mL oven-dried vial was added Lewis acid Co-catalyst, 1-phenylhept-5-yn-1-one **2.21a** (37.2 mg, 0.2 mmol), $B(C_6F_5)_3$, PMP, and solvent (1.0 mL) under nitrogen atmosphere. The resulting mixture was allowed to stir at 22 °C or 80 °C for 12 h. Upon completion, the reaction mixture was diluted with CH_2Cl_2, and concentrated *in vacuo*. The product yield was determined by the ^1H NMR analysis of the unpurified product mixture using mesitylene as the internal standard.

Experimental Procedure for Optimization of BOX Ligands (See Table 2.3, Table 2.4 and Table 2.5)

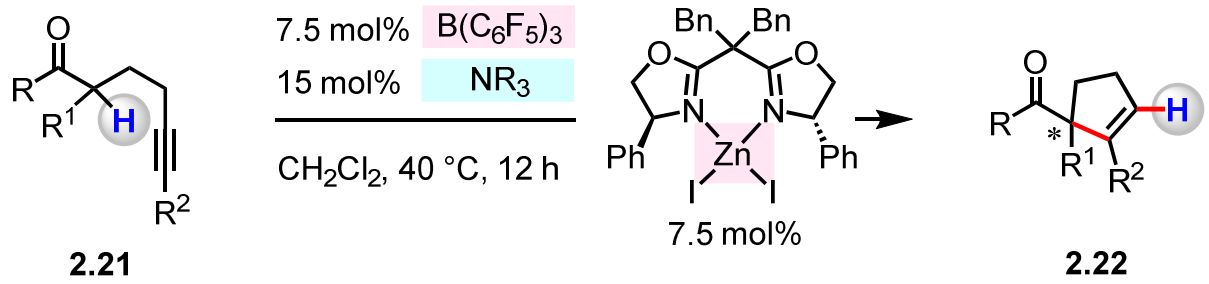
To a 7.0 mL oven-dried vial was added ZnI_2 (0.02 mmol, 10 mol%), ligand (0.022 mmol, 11 mol%), CH_2Cl_2 (0.5 mL) under nitrogen atmosphere. The mixture was allowed to stir for 30 minutes at 22 °C. Subsequently, **2.21a** or **2.21c** (0.20 mmol), $B(C_6F_5)_3$ (0.02 mmol), PMP (0.04 mmol), and CH_2Cl_2 (0.5 mL) were added to the vial under nitrogen atmosphere, and the resulting mixture was allowed to stir at 22 °C for 12 h. Upon completion, the reaction mixture was diluted with CH_2Cl_2, concentrated *in vacuo*. The product yield was determined by the ^1H NMR analysis of the unpurified product mixture using mesitylene as the internal standard. The product was purified by preparative TLC (hexanes:EtOAc = 10:1). The er values of product **2.22a** or **2.22c** was determined by HPLC analysis of the isolated and purified product.

Experimental Procedure for Optimization of Reaction Parameters for Sequential Conia-Ene-Type Cyclizations/Negishi Coupling Reaction (see Tables 2.8)

To a 7.0 mL oven-dried vial was added, 1-phenylhept-5-yn-1-one **2.21a** (18.6 mg, 0.10 mmol), iodobenzene **2.27a** (24.5 mg, 0.12 mmol**),** $B(C_6F_5)_3$, PMP, ZnI_2, $Pd(PPh_3)_4$ and CH_2Cl_2 (0.5 mL) under nitrogen atmosphere. The resulting mixture was allowed to stir at 22 °C for 12 h. Upon completion, the reaction mixture was diluted with CH_2Cl_2, and concentrated *in vacuo*. The product yield was determined by the ^1H NMR analysis of the unpurified product mixture using mesitylene as the internal standard.

2.6.2.4 General Procedures for the Enantioselective Conia-Ene-Type Reaction (See Table 2.6 and Table 2.7)

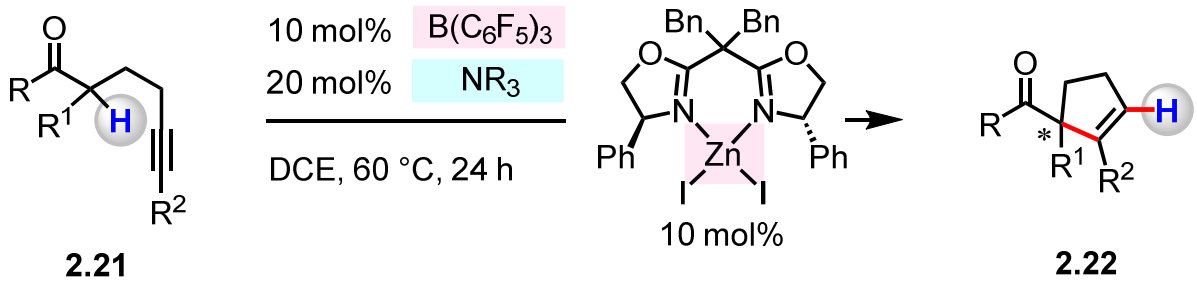
General Procedure C



2.21 **2.22**

To a 7.0 mL oven-dried vial was added substrate **2.21** (0.2 mmol), ZnI_2/**L10** (7.5 mol%), $B(C_6F_5)_3$ (7.5 mol%), PMP or *N*-methylpiperidine (15 mol%), and CH_2Cl_2 (1.0 mL) under nitrogen atmosphere. The resulting mixture was allowed to stir at 40 °C for 12 h. Upon completion, the reaction mixture was diluted with CH_2Cl_2, concentrated *in vacuo* and purified by silica gel column chromatography.

General Procedure D



2.21 **2.22**

To a 7.0 mL oven-dried vial was added substrate **2.21** (0.2 mmol), ZnI_2/**L10** (10 mol%), $B(C_6F_5)_3$ (10 mol%), PMP or *N*-methylpiperidine (20 mol%), and DCE (1.0 mL) under nitrogen atmosphere. The resulting mixture was allowed to stir at 60 °C for 24 h. Upon completion, the reaction mixture was diluted with CH_2Cl_2, concentrated *in vacuo* and purified by silica gel column chromatography.

2.6.2.5 General Procedures for Sequential Conia-Ene-Type Cyclizations/Negishi Coupling Reaction (see Tables 2.9)

General Procedure E

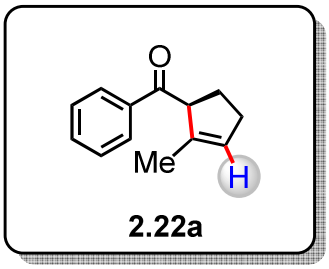
2.21 **2.27** **2.28**

To a 7.0 mL oven-dried vial was added substrate **2.21** (0.10 mmol), aryl iodide **2.27** (0.12 mmol**),** $B(C_6F_5)_3$ (10 mol%), PMP (100 mol%), ZnI_2 (50 mol%), $Pd(PPh_3)_4$ (1.0 mol%) and CH_2Cl_2 (0.5 mL) under nitrogen atmosphere. The resulting mixture was allowed to stir at 22 °C for 12 h. Upon completion, the reaction mixture was diluted with CH_2Cl_2, concentrated *in vacuo* and purified by silica gel column chromatography.

2.6.2.6 Procedure for Large Scale Reaction

To a 25 mL oven-dried sealed tube was added substrate 1-phenylnon-5-yn-1-one **2.21c** (1.5 g, 7 mmol), ZnI_2/**L10** (141 mg, 0.175 mmol, 2.5 mol%), $B(C_6F_5)_3$ (179 mg, 0.350 mmol, 5.0 mol%), PMP (109 mg, 0.700 mmol, 10 mol%), and CH_2Cl_2 (10 mL) under nitrogen atmosphere. The resulting mixture was allowed to stir at 40 °C for 24 h. Upon completion, the solvent was removed *in vacuo* and purification by silica gel column chromatography gave the product as a pale yellow oil (1.4 g, 94% yield, 97:3 er). The er value was determined by HPLC analysis of the isolated and purified product.

2.6.3 Analytical Data



(*S*)-(2-Methylcyclopent-2-en-1-yl)(phenyl)methanone (2.22a)

According to the General Procedure **C**, 1-phenylhept-5-yn-1-one **2.21a** (37.2 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using PMP as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % EtOAc in hexanes) to give **2.22a** (35.7 mg, 96%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 (d, J = 8.1 Hz, 2H), 7.56 (t, J = 7.9 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 5.67 – 5.56 (m, 1H), 4.37 (t, J = 7.3 Hz, 1H), 2.53 – 2.43 (m, 1H), 2.43 – 2.30 (m, 2H), 2.14 – 2.05 (m, 1H), 1.70 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.48, 141.63, 140.32, 136.09, 131.93, 131.75, 131.70, 59.32, 34.93, 32.87, 18.98; **IR** (neat) 3057, 2928, 1704, 1674, 1578, 1345, 1175, 1111, 1000, 775, 697 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{13}H_{15}O$ (MH^+): 187.1117; found: 187.1114; **HPLC** (Chiralcel OD-H; 1%/ 99% isopropanol/ hexanes, 0.5 mL/min; tr = 11.5 min (major), 13.6 min (minor); 82:18 er); $[\alpha]^{25}_{D}$ = –36.7° (c = 1.0, CH_2Cl_2). The absolute configuration for this product was assigned in analogy to that determined for product **2.22c**.

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Acq. Instrument : Wasa_LC1                         Location :   81
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                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-04-25 21-13-41\column2 1%IPA 99% hexane 60min-0.
                  5mL.M (Sequence Method)
Last changed    : 4/25/2018 9:13:43 PM by SYSTEM
Method Info     : Column2 60min-1% iPrOH 99% hexane-0.5mL
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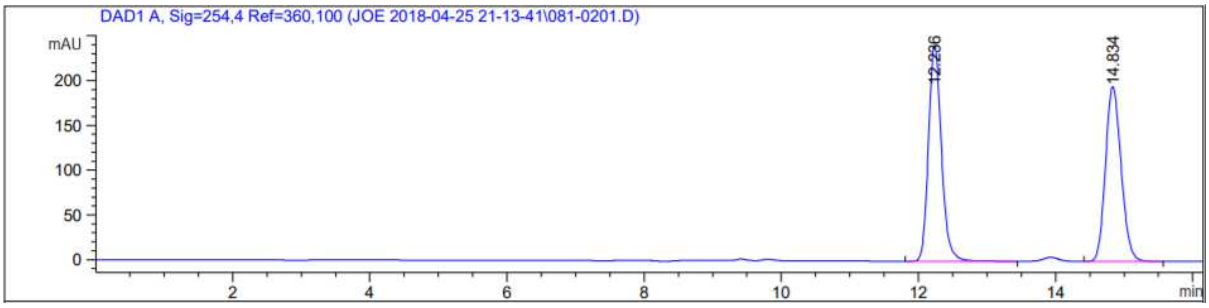

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

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2	14.834	BB	0.2474	3100.15894	195.06850	49.3959
Totals :				6276.15161	435.90872	

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                                                 Inj Volume : 4.000 µl
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                  5mL.M (Sequence Method)
Last changed    : 10/3/2018 6:14:40 PM by SYSTEM
Method Info     : Column3 20min-1% iPrOH 99% hexane-0.5mL

Additional Info : Peak(s) manually integrated
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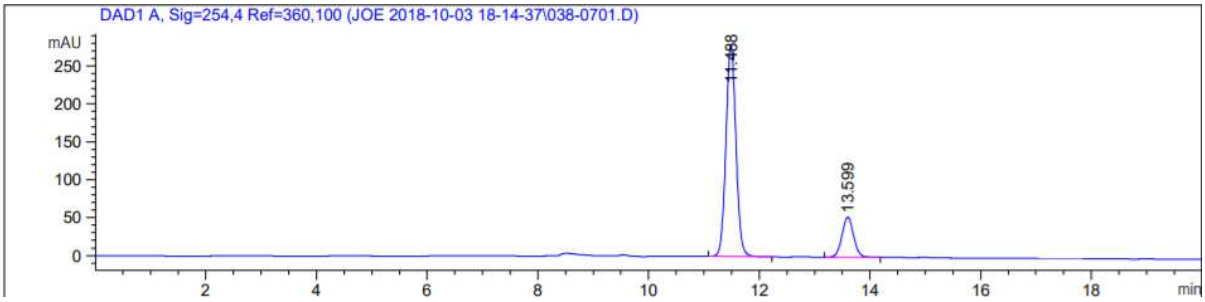

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

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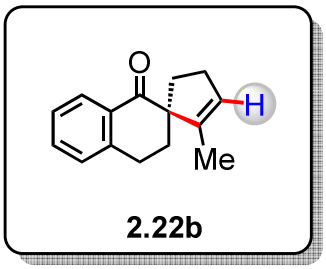
1	11.488	BB	0.1941	3508.73730	280.17123	81.9336
2	13.599	BB	0.2247	773.67737	52.87839	18.0664
Totals :				4282.41467	333.04962	



2.22b

(*R*)-2-Methyl-3',4'-dihydro-1'*H*-spiro[cyclopentane-1,2'-naphthalen]-2-en-1'-one (2.22b)

According to the General Procedure **D**, 2-(pent-3-yn-1-yl)-3,4-dihydronaphthalen-1(2*H*)-one **2.21b** (42.5 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using *N*-methylpiperidine as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % EtOAc in hexanes) to give **2.22b** (31.0 mg, 73%) as a pale yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.05 (d, J = 7.8 Hz, 1H), 7.45 (t, J = 7.4 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.23 (d, J = 7.6 Hz, 1H), 5.65 – 5.60 (m, 1H), 3.19 – 3.09 (m, 1H), 2.96 – 2.87 (m, 1H), 2.40 – 2.34 (m, 1H), 2.34 – 2.29 (m, 1H), 2.11 – 1.99 (m, 2H), 1.91 – 1.80 (m, 1H), 1.65 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 203.14, 146.36, 144.77, 135.78, 134.64, 131.19, 130.64, 130.56, 129.27, 63.82, 36.31, 34.72, 32.34, 28.96, 16.11; **IR** (neat) 2848, 2765, 1674, 1597, 1375, 1216, 1021, 900, 830, 738, 486 cm^{-1}; HRMS (DART) Calcd for $C_{15}H_{15}O$ (MH^+): 213.12739; found: 213.12669; **HPLC** (Chiralcel OD-H; 1%/ 99% isopropanol/ hexanes, 0.5 mL/min; tr = 14.0 min (major), 18.7 min (minor); 91:9 er); $[\alpha]^{25}_{D}$ = –21.1° (c = 1.0, CH_2Cl_2). The absolute configuration for this product was assigned in analogy to that determined for product **2.22c**.

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                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-20 18-49-49\column3 1% IPA 99% hex 30min-0.5ml
                  .M (Sequence Method)
Last changed    : 11/20/2018 6:49:53 PM by SYSTEM
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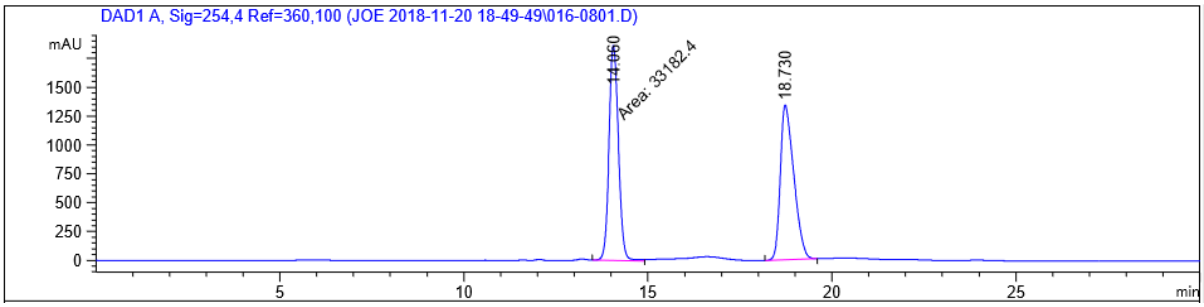

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

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1	14.060	MM	0.2969	3.31824e4	1862.94519	49.2553
2	18.730	BB	0.3908	3.41858e4	1343.65039	50.7447
Totals :				6.73682e4	3206.59558	

```
Acq. Operator   : SYSTEM                          Seq. Line :   9
Acq. Instrument : Wasa_LC1                         Location :   17
Injection Date  : 11/20/2018 11:49:25 PM               Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-20 18-49-49\column3 1% IPA 99% hex 30min-0.5ml
                  .M (Sequence Method)
Last changed    : 11/20/2018 6:49:53 PM by SYSTEM
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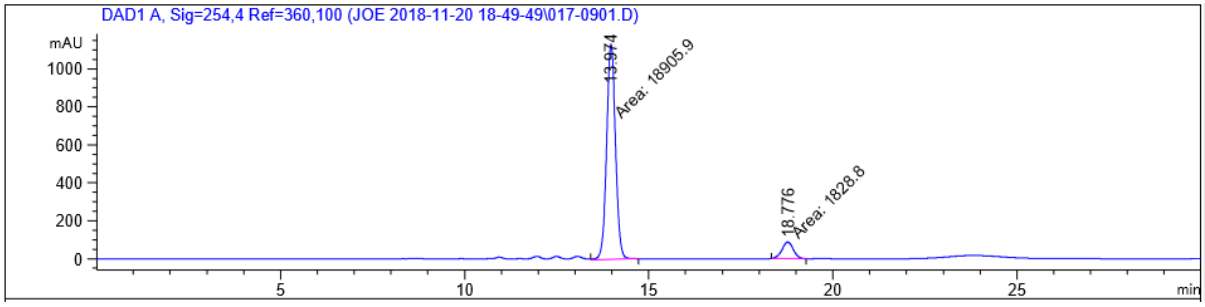
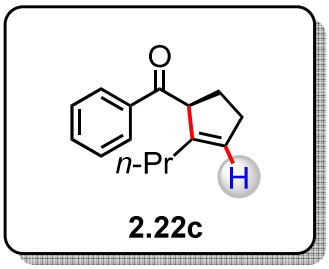


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.974	MM	0.2783	1.89059e4	1132.41357	91.1800
2	18.776	MM	0.3532	1828.79651	86.29856	8.8200
Totals :				2.07347e4	1218.71214	



2.22c

(*S*)-Phenyl(2-propylcyclopent-2-en-1-yl)methanone (2.22c)

According to the General Procedure **C**, 1-phenylnon-5-yn-1-one **2.21c** (42.9 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using PMP as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % EtOAc in hexanes) to give **2.22c** (42.0 mg, 98%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.1 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 5.71 – 5.58 (m, 1H), 4.42 (t, *J* = 7.6 Hz, 1H), 2.55 – 2.44 (m, 1H), 2.44 – 2.37 (m, 1H), 2.37 – 2.26 (m, 1H), 2.12 – 2.00 (m, 2H), 2.00 – 1.89 (m, 1H), 1.52 – 1.35 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.56, 143.21, 137.18, 132.88, 128.57, 128.48, 127.29, 54.88, 32.12, 31.65, 29.68, 20.89, 13.98; **IR** (neat) 2956, 2929, 2869, 1707, 1676, 1447, 1314, 1258, 1069, 710, 699 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{15}H_{19}O$ (MH^+): 215.1430; found: 215.1427; **HPLC** (Chiralcel OD-H; 1%/ 99% isopropanol/ hexanes, 0.5 mL/min; tr = 9.8 min (major), 10.9 min (minor); 97:3 er). $[\alpha]^{25}_{D} = -19.6°$ (c = 1.0, CH_2Cl_2). For the determination of absolute configuration, see section **2.6.4**.

```
Acq. Operator   : SYSTEM                          Seq. Line :   1
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Injection Date  : 9/19/2018 2:20:51 PM                 Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-09-19 14-19-45\column3 1%IPA 99% hexane 20min-0.
                  5mL.M (Sequence Method)
Last changed    : 9/19/2018 2:19:47 PM by SYSTEM
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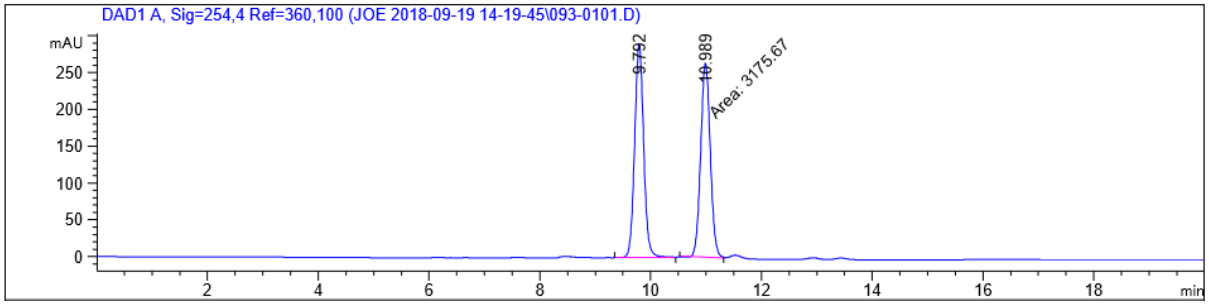

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.792	BB	0.1738	3275.03320	289.89484	50.7702
2	10.989	MM	0.2007	3175.66724	263.68991	49.2298
Totals :				6450.70044	553.58475	

```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                         Location :   32
Injection Date  : 10/3/2018 6:37:25 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-10-03 18-14-37\column3 1%IPA 99% hexane 20min-0.
                  5mL.M (Sequence Method)
Last changed    : 10/3/2018 6:14:40 PM by SYSTEM
Method Info     : Column3 20min-1% iPrOH 99% hexane-0.5mL
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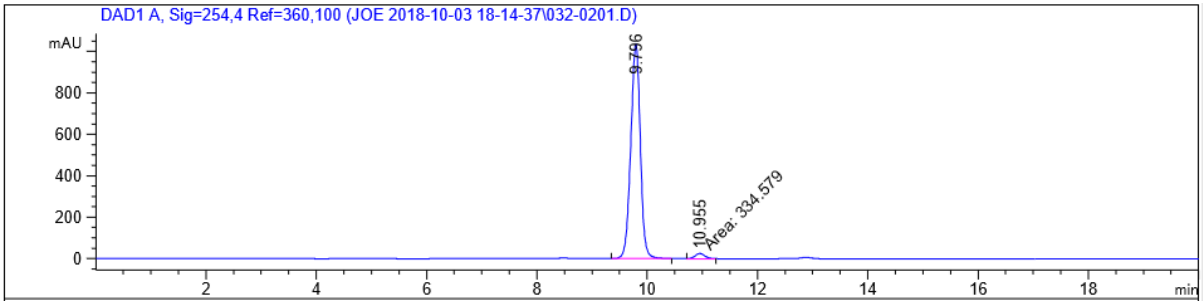
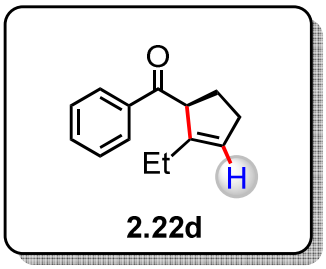


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.796	BB	0.1868	1.24999e4	1035.63757	97.3931
2	10.955	MM	0.2156	334.57858	25.86999	2.6069
Totals :				1.28345e4	1061.50756	



2.22d

(S)-(2-Ethylcyclopent-2-en-1-yl)(phenyl)methanone (2.22d)

According to the General Procedure **C**, 1-phenyloct-5-yn-1-one **2.21d** (40.0 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using PMP as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % EtOAc in hexanes) to give **2.22d** (38.0 mg, 95%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 5.64 (q, J = 1.8 Hz, 1H), 4.43 (t, J = 7.8 Hz, 1H), 2.57 – 2.45 (m, 1H), 2.44 – 2.26 (m, 2H), 2.16 – 2.03 (m, 2H), 2.01 – 1.88 (m, 1H), 1.03 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.57, 144.90, 137.21, 132.88, 128.57, 128.49, 126.31, 55.04, 31.62, 29.66, 23.10, 12.20; **IR** (neat) 2933, 2876, 2850, 1706, 1675, 1446, 1272, 1023, 1001, 700, 647 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{14}H_{17}O$ (MH^+): 201.1274; found: 201.1264; **HPLC** (Chiralcel OD-H; 1%/ 99% isopropanol/ hexanes, 0.5 mL/min; tr = 10.3 min (major), 12.4 min (minor); 96:4 er); $[\alpha]^{25}_{D}$ = –23.1° (c = 1.0, CH_2Cl_2). The absolute configuration for this product was assigned in analogy to that determined for product **2.22c**.

```
Acq. Operator   : SYSTEM                          Seq. Line :   1
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Injection Date  : 10/21/2018 12:36:49 PM               Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-10-21 12-34-50\column3 1% IPA 99% hex 30min-0.5ml
                  .M (Sequence Method)
Last changed    : 10/21/2018 12:34:53 PM by SYSTEM
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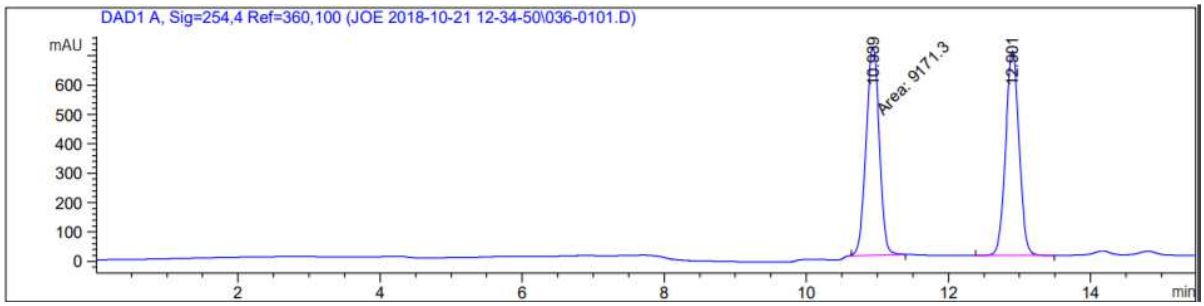

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.939	MM	0.2154	9171.29590	709.54291	50.0187
2	12.901	BB	0.2054	9164.42090	696.77075	49.9813
Totals :				1.83357e4	1406.31366	

```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Wasa_LC1                         Location :   37
Injection Date  : 10/21/2018 12:54:27 PM               Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-10-21 12-53-19\column3 1%IPA 99% hexane 20min-0.
                  5mL.M (Sequence Method)
Last changed    : 10/21/2018 12:53:22 PM by SYSTEM
Method Info     : Column3 20min-1% iPrOH 99% hexane-0.5mL
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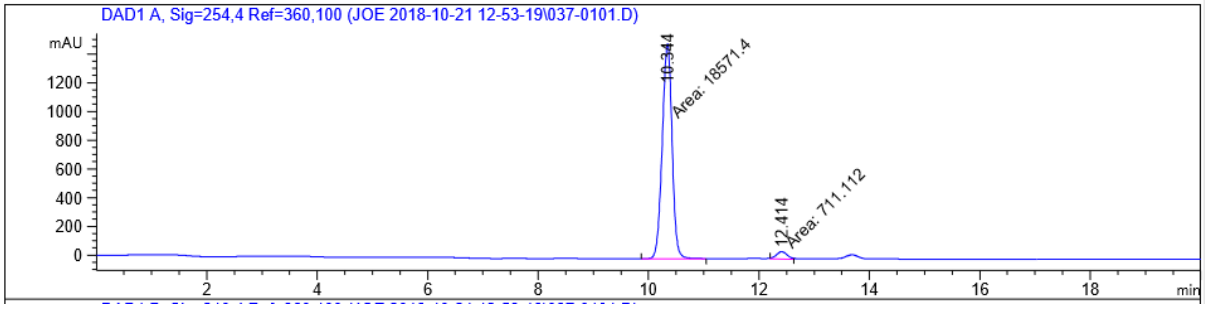
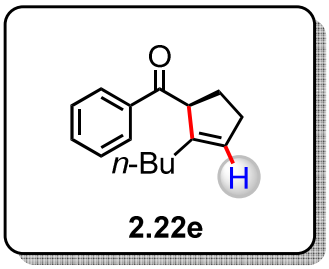


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.344	MM	0.2068	1.85714e4	1496.42065	96.3121
2	12.414	MM	0.2292	711.11157	51.71229	3.6879
Totals :				1.92825e4	1548.13294	



2.22e

(*S*)-(2-Butylcyclopent-2-en-1-yl)(phenyl)methanone (2.22e)

According to the General Procedure **C**, 1-phenyldec-5-yn-1-one **2.21e** (45.7 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using PMP as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % EtOAc in hexanes) to give **2.22e** (45.2 mg, 99%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.1 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 5.64 (d, *J* = 1.6 Hz, 1H), 4.42 (t, *J* = 7.9 Hz, 1H), 2.54 – 2.44 (m, 1H), 2.44 – 2.28 (m, 2H), 2.15 – 2.01 (m, 2H), 1.99 – 1.89 (m, 1H), 1.45 – 1.35 (m, 2H), 1.33 – 1.18 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.57, 143.40, 137.20, 132.87, 128.56, 128.49, 127.14, 54.94, 31.64, 29.88, 29.66, 22.52, 13.89; **IR** (neat) 2953, 2927, 2857, 1707, 1676, 1342, 1109, 931, 859, 699, 669 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{16}H_{21}O$ (MH^+): 229.1587; found: 229.1582; **HPLC** (Chiralcel OD-H; 1%/ 99% isopropanol/ hexanes, 0.5 mL/min; tr = 9.7 min (major), 10.3 min (minor); 97:3 er); $[\alpha]^{25}_{D} = -31.4°$ (c = 1.0, CH_2Cl_2). The absolute configuration for this product was assigned in analogy to that determined for product **2.22c**.

```
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Injection Date  : 11/19/2018 2:32:22 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-19 14-30-30\column3 1%IPA 99% hexane 20min-0.
                  5mL.M (Sequence Method)
Last changed    : 11/19/2018 2:30:33 PM by SYSTEM
Method Info     : Column3 20min-1% iPrOH 99% hexane-0.5mL
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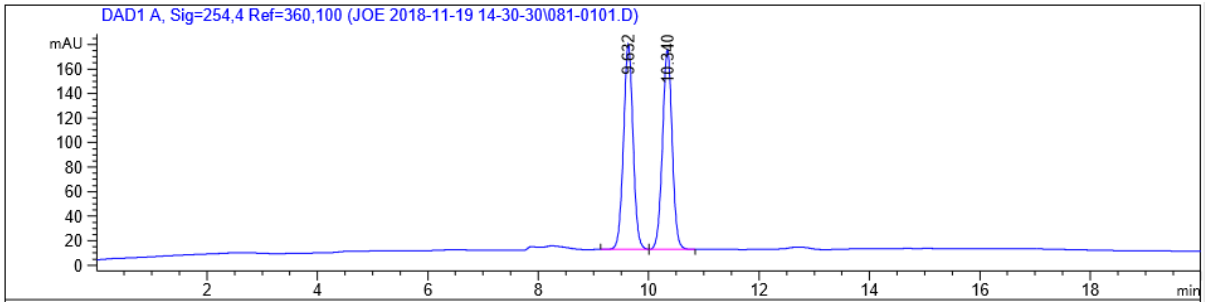

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.632	BB	0.1864	2012.38794	167.17357	50.2800
2	10.340	BB	0.1886	1989.97559	162.84615	49.7200
Totals :				4002.36353	330.01971	

```
Acq. Operator   : SYSTEM                          Seq. Line :   4
Acq. Instrument : Wasa_LC1                         Location :   24
Injection Date  : 10/3/2018 5:27:12 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-10-03 16-22-34\column3 1%IPA 99% hexane 20min-0.
                  5mL.M (Sequence Method)
Last changed    : 10/3/2018 4:22:36 PM by SYSTEM
Method Info     : Column3 20min-1% iPrOH 99% hexane-0.5mL
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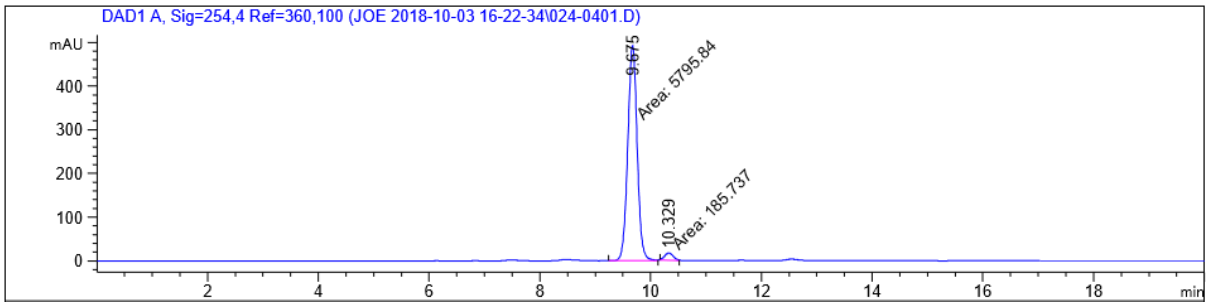
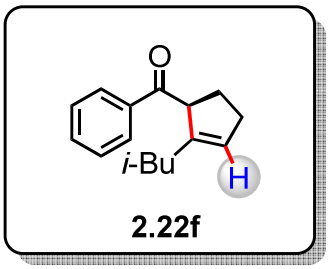


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.675	MM	0.1962	5795.84131	492.23010	96.8949
2	10.329	MM	0.1835	185.73660	16.87234	3.1051
Totals :				5981.57791	509.10244	



2.22f

(*S*)-(2-Isobutylcyclopent-2-en-1-yl)(phenyl)methanone (2.22f)

According to the General Procedure **D**, 8-methyl-1-phenylnon-5-yn-1-one **2.21f** (45.7 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using PMP as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % EtOAc in hexanes) to give **2.22f** (44.4 mg, 97%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (d, J = 7.1 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 5.86 – 5.45 (m, 1H), 4.40 (t, J = 7.5 Hz, 1H), 2.56 – 2.44 (m, 1H), 2.44 – 2.27 (m, 2H), 2.10 – 1.99 (m, 1H), 1.96 – 1.89 (m, 2H), 1.74 – 1.62 (m, 1H), 0.97 – 0.70 (m, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.55, 142.17, 137.20, 132.87, 128.67, 128.57, 128.48, 54.68, 39.35, 31.61, 29.75, 26.42, 23.14, 22.06; **IR** (neat) 2949, 2924, 2864, 1676, 1461, 1445, 1364, 1205, 958, 849, 779 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{16}H_{21}O$ (MH^+): 229.1587; found: 229.1576; **HPLC** (Chiralcel OD-H; 1%/ 99% isopropanol/ hexanes, 0.5 mL/min; tr = 9.2 min (major), 9.9 min (minor); 96:4 er); $[\alpha]^{25}_{D}$ = –24.9° (c = 1.0, CH_2Cl_2). The absolute configuration for this product was assigned in analogy to that determined for product **2.22c**.

```
Acq. Operator   : SYSTEM                          Seq. Line :   4
Acq. Instrument : Wasa_LC1                         Location :   12
Injection Date  : 11/20/2018 9:34:41 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-20 18-49-49\column3 1%IPA 99% hexane 20min-0.
                  5mL.M (Sequence Method)
Last changed    : 11/20/2018 6:49:53 PM by SYSTEM
Method Info     : Column3 20min-1% iPrOH 99% hexane-0.5mL
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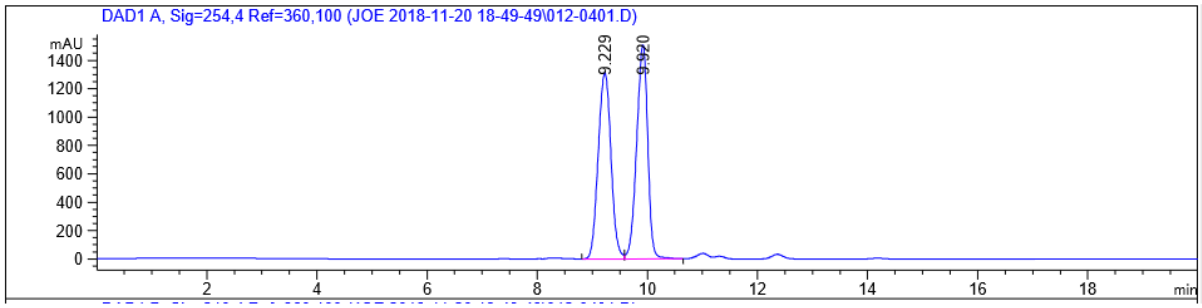

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.229	BV	0.2560	2.11567e4	1313.11548	50.0211
2	9.920	VB	0.2194	2.11388e4	1508.86450	49.9789
Totals :				4.22955e4	2821.97998	

```
Acq. Operator   : SYSTEM                          Seq. Line :   5
Acq. Instrument : Wasa_LC1                         Location :   13
Injection Date  : 11/20/2018 9:55:37 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-20 18-49-49\column3 1%IPA 99% hexane 20min-0.
                  5mL.M (Sequence Method)
Last changed    : 11/20/2018 6:49:53 PM by SYSTEM
Method Info     : Column3 20min-1% iPrOH 99% hexane-0.5mL
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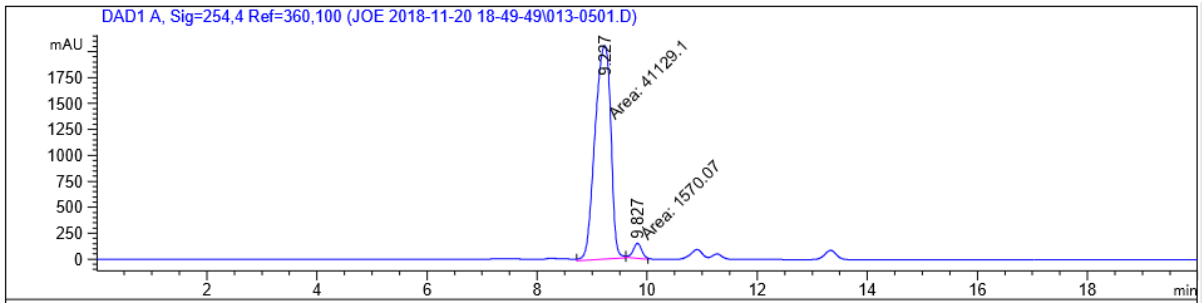
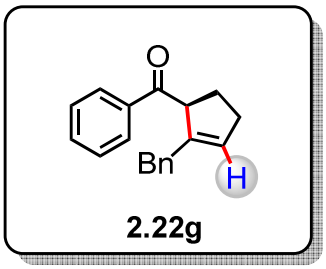


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.227	MM	0.3331	4.11291e4	2058.13403	96.3230
2	9.827	MM	0.1823	1570.07068	143.57298	3.6770
Totals :				4.26992e4	2201.70702	



(*S*)-(2-Benzylcyclopent-2-en-1-yl)(phenyl)methanone (2.22g)

According to the General Procedure **D**, 1,7-diphenylhept-5-yn-1-one **2.21g** (52.5 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using PMP as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % EtOAc in hexanes) to give **2.22g** (43.2 mg, 80%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88 (d, J = 7.4 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.7 Hz, 2H), 7.23 (dd, J = 13.4, 6.3 Hz, 2H), 7.16 (t, J = 7.3 Hz, 1H), 7.09 (d, J = 7.2 Hz, 2H), 5.62 (s, 1H), 4.38 – 4.25 (m, 1H), 3.56 (d, J = 15.5 Hz, 1H), 3.23 (d, J = 15.4 Hz, 1H), 2.56 – 2.44 (m, 1H), 2.44 – 2.27 (m, 2H), 2.10 – 2.01 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.41, 142.36, 139.41, 137.03, 132.92, 129.75, 128.98, 128.53, 128.51, 128.29, 126.03, 53.91, 36.64, 31.59, 29.79; **IR** (neat) 3058, 3024, 2931, 1674, 1594, 1447, 1211, 1072, 1025, 758, 700 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{19}H_{19}O$ (MH^+): 263.1430; found: 263.1431; **HPLC** (Chiralcel OD-H; 1%/ 99% isopropanol/ hexanes, 0.5 mL/min; tr = 12.1 min (minor) , 13.2 min (major); 98:2 er); $[\alpha]^{25}_{D} = -14.1°$ (c = 1.0, CH_2Cl_2). The absolute configuration for this product was assigned in analogy to that determined for product **2.22c**.

```
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Acq. Instrument : Wasa_LC1                         Location :   14
Injection Date  : 11/21/2018 7:54:09 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-21 19-21-58\column3 1% IPA 99% hex 30min-0.5ml
                  .M (Sequence Method)
Last changed    : 11/21/2018 7:22:01 PM by SYSTEM
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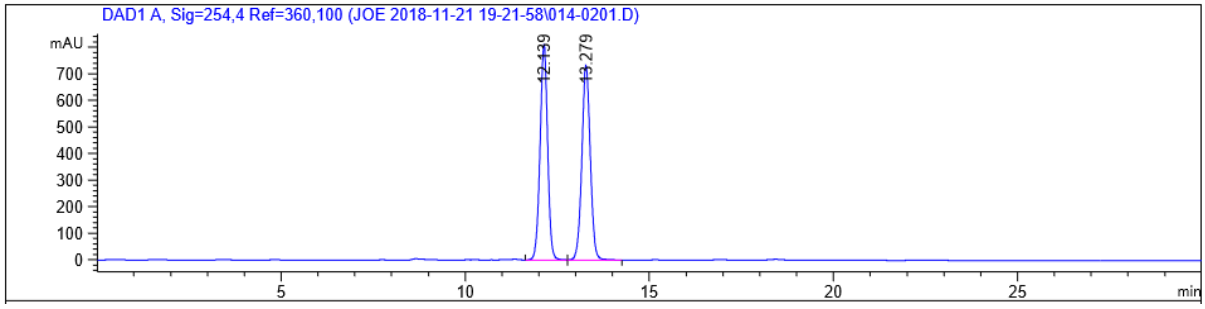

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

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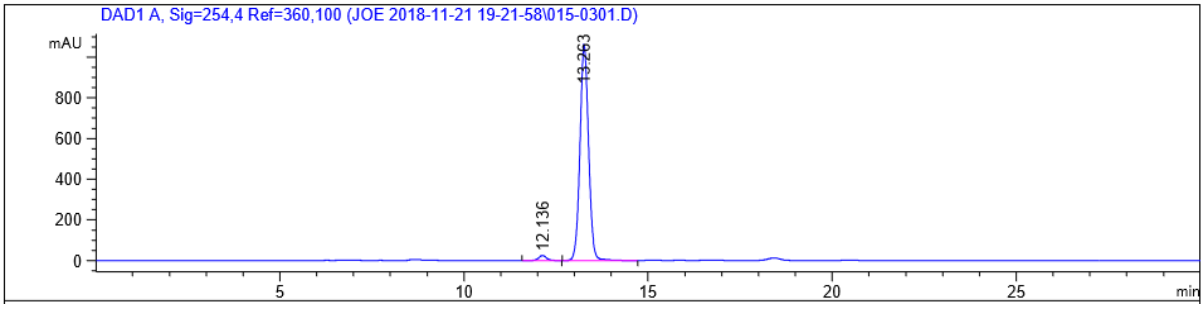
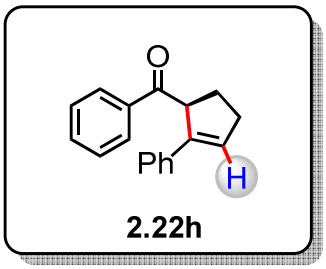
1	12.139	BB	0.2206	1.15781e4	810.85712	49.8138
2	13.279	BB	0.2459	1.16646e4	732.01556	50.1862
Totals :				2.32427e4	1542.87268	

```
Acq. Operator   : SYSTEM                          Seq. Line :   3
Acq. Instrument : Wasa_LC1                         Location :   15
Injection Date  : 11/21/2018 8:25:05 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-21 19-21-58\column3 1% IPA 99% hex 30min-0.5ml
                  .M (Sequence Method)
Last changed    : 11/21/2018 7:22:01 PM by SYSTEM
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.136	BB	0.2262	384.82883	25.77525	2.1771
2	13.263	BB	0.2520	1.72918e4	1062.03174	97.8229
Totals :				1.76766e4	1087.80699	



2.22h

(*S*)-Phenyl(2-phenylcyclopent-2-en-1-yl)methanone (2.22h)

According to the General Procedure **D**, 1,6-diphenylhex-5-yn-1-one **2.21h** (49.6 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using PMP as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % Et_2O in hexanes) to give **2.22h** (24.8 mg, 50%) as a colorless solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 2H), 7.22 (t, *J* = 7.7 Hz, 2H), 7.16 (t, *J* = 7.3 Hz, 1H), 6.49 – 6.44 (m, 1H), 4.95 (d, *J* = 11.7 Hz, 1H), 2.73 – 2.50 (m, 3H), 2.17 – 2.10 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 201.11, 141.64, 136.52, 135.57, 133.05, 130.12, 128.69, 128.65, 128.37, 127.07, 125.78, 53.48, 32.39, 30.06; **IR** (neat) 3052, 3025, 2937, 2843, 1678, 1577, 1445, 1207, 980, 752, 690 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{18}H_{17}O$ (MH^+): 249.12739; found: 249.12799; **HPLC** (Chiralcel OD-H; 1%/ 99% isopropanol/ hexanes, 0.5 mL/min; tr = 20.6 min (minor), 26.6 min (major); 91:9 er); $[\alpha]^{25}_{D} = -34.6°$ (c = 1.0, CH_2Cl_2). The absolute configuration for this product was assigned in analogy to that determined for product **2.22c**.

```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                         Location :   1
Injection Date  : 11/7/2018 5:02:17 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-07 16-29-27\column3 1% IPA 99% hex 30min-0.5ml
                  .M (Sequence Method)
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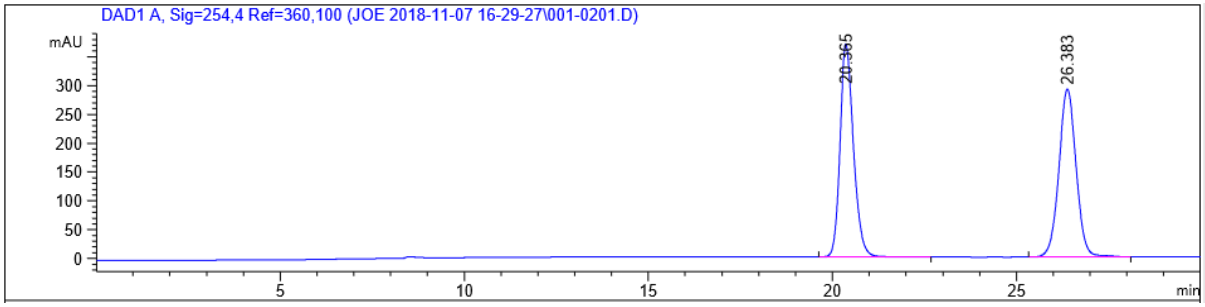
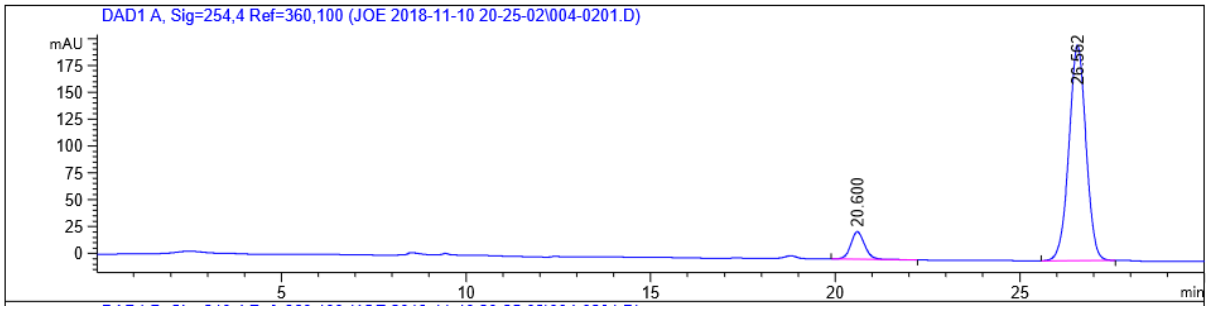


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

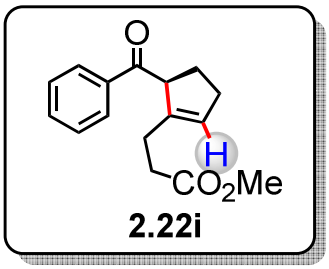
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.365	BB	0.3859	9365.00684	369.26086	49.7099
2	26.383	BB	0.4997	9474.31641	291.10678	50.2901
Totals :				1.88393e4	660.36765	

```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                         Location :   4
Injection Date  : 11/10/2018 8:57:07 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-10 20-25-02\column3 1% IPA 99% hex 30min-0.5ml
                  .M (Sequence Method)
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.600	BB	0.4007	677.84796	25.78904	9.5297
2	26.562	BB	0.4927	6435.16357	200.36926	90.4703
Totals :				7113.01154	226.15830	



2.22i

Methyl (*S*)-3-(5-benzoylcyclopent-1-en-1-yl)propanoate (2.22i)

According to the General Procedure **C**, methyl 9-oxo-9-phenylnon-4-ynoate **2.21i** (51.7 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using PMP as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % EtOAc in hexanes) to give **2.22i** (50.1 mg, 97%) as a colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.00 (d, J = 8.0 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 5.66 (s, 1H), 4.45 (d, J = 7.1 Hz, 1H), 3.63 (s, 3H), 2.54 – 2.44 (m, 3H), 2.44 – 2.35 (m, 3H), 2.34 – 2.27 (m, 1H), 2.13 – 1.96 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 204.66, 176.22, 144.01, 139.51, 135.69, 131.29, 131.18, 130.66, 57.68, 54.19, 35.13, 34.31, 32.34, 27.85; **IR** (neat) 2920, 2849, 1734, 1676, 1445, 1342, 1208, 1162, 1000, 701, 670 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{16}H_{19}O_3$ (MH^+): 259.1329; found: 259.1335; **HPLC** (Chiralcel OD-H; 5%/ 95% isopropanol/ hexanes, 1.0 mL/min; tr = 10.3 min (minor), 24.6 min (major); 94:6 er); $[\alpha]^{25}_D$ = +1.7° (c = 1.0, CH_2Cl_2). The absolute configuration for this product was assigned in analogy to that determined for product **2.22c**.

```
Acq. Operator   : SYSTEM                          Seq. Line :   9
Acq. Instrument : Wasa_LC1                         Location :   1
Injection Date  : 11/16/2018 6:02:44 AM                Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2018-11-15 21-53-08\column3 5% IPA 95% hex 60min-1.0ml
                  .M
Last changed    : 11/15/2018 9:53:12 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2018-11-15 21-53-08\column3 5% IPA 95% hex 60min-1.0ml
                  .M (Sequence Method)
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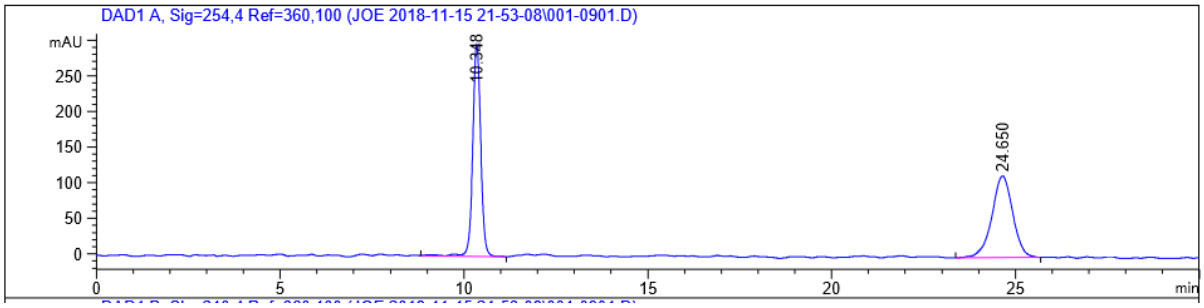
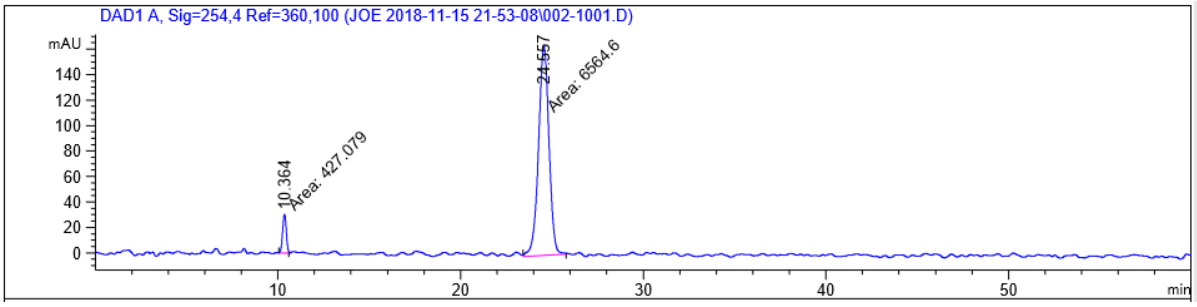


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

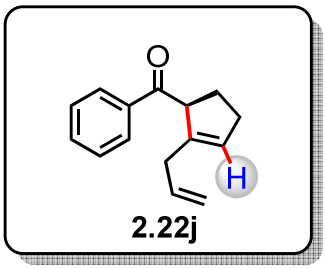
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.348	VB R	0.2295	4508.04883	297.70328	49.9701
2	24.650	BB	0.5998	4513.44385	114.50896	50.0299
Totals :				9021.49268	412.21224	

```
Acq. Operator   : SYSTEM                          Seq. Line :  10
Acq. Instrument : Wasa_LC1                         Location :   2
Injection Date  : 11/16/2018 7:03:40 AM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-15 21-53-08\column3 5% IPA 95% hex 60min-1.0ml
                  .M (Sequence Method)
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.364	MM	0.2324	427.07898	30.62230	6.1084
2	24.557	MM	0.6627	6564.60205	165.10117	93.8916
Totals :				6991.68103	195.72347	



(*S*)-(2-Allylcyclopent-2-en-1-yl)(phenyl)methanone (2.22j)

According to the General Procedure **C**, 1-phenylnon-8-en-5-yn-1-one **2.21j** (42.5 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using PMP as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % Et_2O in hexanes) to give **2.22j** (40.0 mg, 94%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.7 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 5.87 – 5.74 (m, 1H), 5.72 – 5.64 (m, 1H), 5.02 – 4.89 (m, 2H), 4.44 (t, *J* = 7.5 Hz, 1H), 2.91 (dd, *J* = 16.3, 6.0 Hz, 1H), 2.70 (dd, *J* = 16.2, 7.5 Hz, 1H), 2.55 – 2.45 (m, 1H), 2.44 – 2.30 (m, 2H), 2.11 – 2.00 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.29, 141.28, 137.10, 135.78, 132.95, 128.80, 128.57, 128.52, 116.14, 54.42, 34.61, 31.68, 29.68; **IR** (neat) 3059, 2936, 1711, 1674, 1578, 1407, 1211, 1177, 1000, 861, 700 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{15}H_{17}O$ (MH^+): 213.12739; found: 213.12726; **HPLC** (Chiralcel OD-H; 0.3%/ 99.7% isopropanol/ hexanes, 0.5 mL/min; tr = 30.4 min (major), 32.2 min (minor); 97:3 er); $[\alpha]^{25}{}_D$ = −1.5° (c = 1.0, CH_2Cl_2). The absolute configuration for this product was assigned in analogy to that determined for product **2.22c**.

```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                         Location :   53
Injection Date  : 10/15/2018 6:05:25 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2018-10-15 17-02-32\column3 0.3% IPA 99.7% hex 60min-0
                  .5ml.M
Last changed    : 10/15/2018 5:02:35 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2018-10-15 17-02-32\column3 0.3% IPA 99.7% hex 60min-0
                  .5ml.M (Sequence Method)
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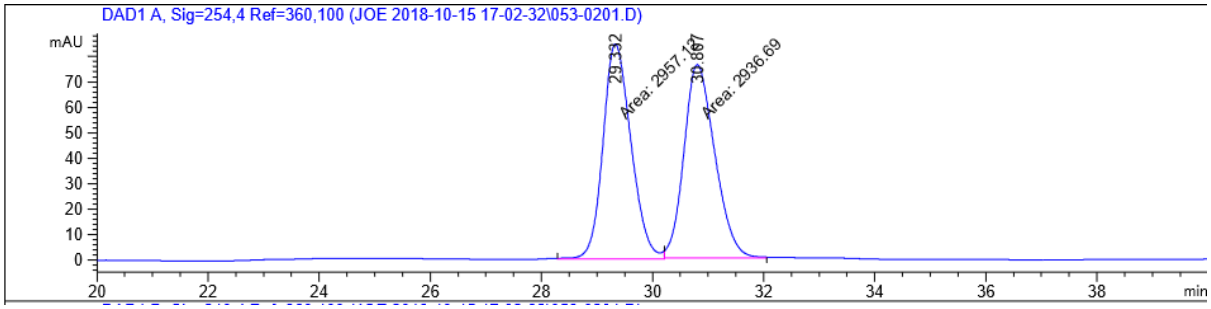

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.332	MM	0.5842	2957.11914	84.36610	50.1733
2	30.807	MM	0.6442	2936.69336	75.97674	49.8267
Totals :				5893.81250	160.34284	

```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                         Location :   62
Injection Date  : 10/15/2018 7:43:43 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2018-10-15 19-01-41\column3 0.3% IPA 99.7% hex 40min-0
                  .5ml.M
Last changed    : 10/15/2018 7:01:44 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2018-10-15 19-01-41\column3 0.3% IPA 99.7% hex 40min-0
                  .5ml.M (Sequence Method)
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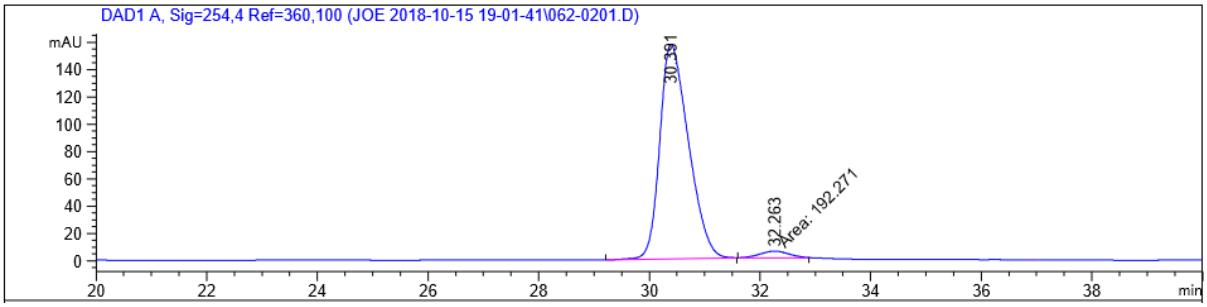
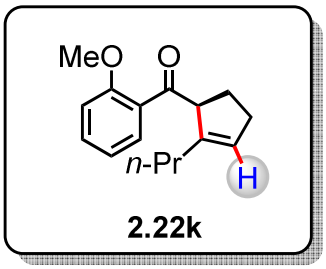


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.391	BB	0.5504	5657.95703	157.00883	96.7134
2	32.263	MM	0.6373	192.27145	5.02845	3.2866
Totals :				5850.22849	162.03728	



2.22k

(*S*)-(2-Methoxyphenyl)(2-propylcyclopent-2-en-1-yl)methanone (2.22k)

According to the General Procedure **C**, 1-(2-methoxyphenyl)non-5-yn-1-one **2.21k** (48.9 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using PMP as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % EtOAc in hexanes) to give **2.22k** (46.4 mg, 95%) as a colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.55 (d, J = 9.1 Hz, 1H), 7.44 (t, J = 7.0 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 5.62 – 5.55 (m, 1H), 4.48 – 4.36 (m, 1H), 3.89 (s, 3H), 2.48 – 2.38 (m, 1H), 2.35 – 2.27 (m, 1H), 2.26 – 2.19 (m, 1H), 2.09 – 2.00 (m, 2H), 1.97 – 1.89 (m, 1H), 1.48 – 1.35 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 206.35, 158.03, 143.88, 132.81, 129.91, 129.87, 127.03, 120.67, 111.44, 59.09, 55.48, 32.16, 31.37, 29.38, 20.84, 14.02; **IR** (neat) 2954, 2928, 2867, 2847, 1671, 1595, 1483, 1462, 1435, 1281, 1243, 1021, 999, 754 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{16}H_{21}O_2$ (MH^+): 245.15361; found: 245.15409; **HPLC** (Chiralcel OD-H; 1%/ 99% isopropanol/ hexanes, 0.5 mL/min; tr = 14.6 min (major), 16.4 min (minor); 93:7 er); $[\alpha]^{25}_D$ = –45.0° (c = 1.0, CH_2Cl_2). The absolute configuration for this product was assigned in analogy to that determined for product **2.22c**.

```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Wasa_LC1                         Location :   4
Injection Date  : 11/19/2018 12:44:02 PM               Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-19 12-42-07\column3 1%IPA 99% hexane 20min-0.
                  5mL.M (Sequence Method)
Last changed    : 11/19/2018 12:42:10 PM by SYSTEM
Method Info     : Column3 20min-1% iPrOH 99% hexane-0.5mL
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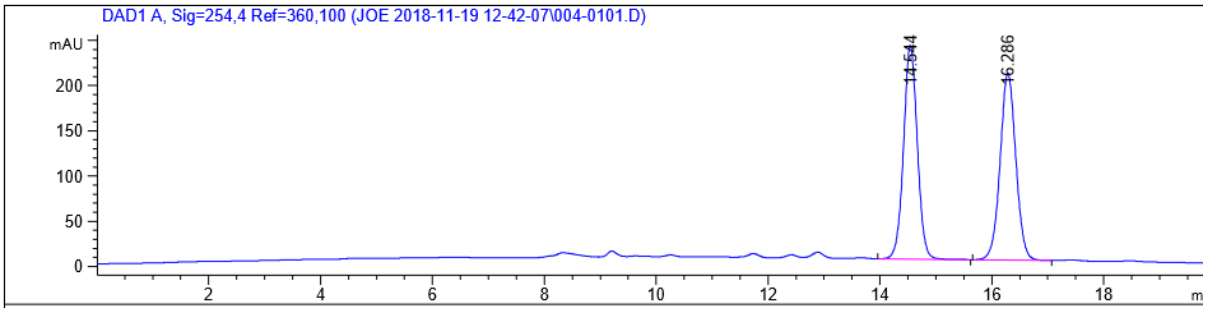
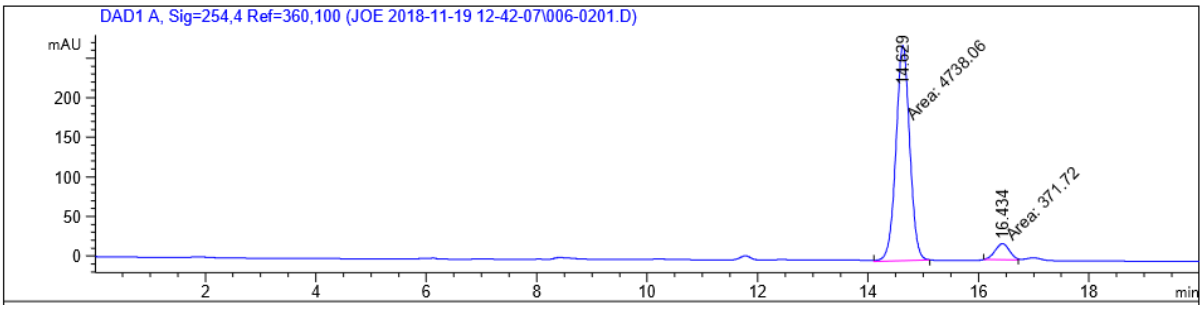


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

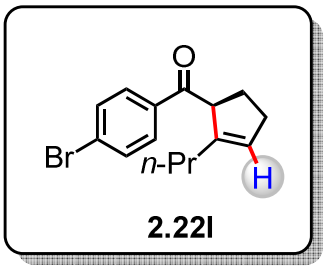
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.544	BB	0.2614	4036.94409	236.15048	49.9895
2	16.286	BB	0.2999	4038.64795	206.78905	50.0105
Totals :				8075.59204	442.93953	

```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                         Location :   6
Injection Date  : 11/19/2018 1:05:00 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-19 12-42-07\column3 1%IPA 99% hexane 20min-0.
                  5mL.M (Sequence Method)
Last changed    : 11/19/2018 12:42:10 PM by SYSTEM
Method Info     : Column3 20min-1% iPrOH 99% hexane-0.5mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.629	MM	0.2901	4738.06152	272.17316	92.7253
2	16.434	MM	0.3035	371.71957	20.41248	7.2747
Totals :				5109.78110	292.58564	



(*S*)-(4-Bromophenyl)(2-propylcyclopent-2-en-1-yl)methanone (2.22l)

According to the General Procedure **C**, 1-(2-methoxyphenyl)non-5-yn-1-one **2.21l** (58.6 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using PMP as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % EtOAc in hexanes) to give **2.22l** (56.8 mg, 97%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.6 Hz, 2H), 7.61 (d, J = 8.7 Hz, 2H), 5.67 – 5.59 (m, 1H), 4.41 – 4.25 (m, 1H), 2.53 – 2.45 (m, 1H), 2.43 – 2.26 (m, 2H), 2.09 – 1.98 (m, 2H), 1.97 – 1.87 (m, 1H), 1.51 – 1.35 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 201.52, 142.93, 135.83, 131.89, 130.03, 128.08, 127.52, 55.00, 32.10, 31.64, 29.55, 20.87, 13.96; **IR** (neat) 2956, 2928, 2869, 1706, 1675, 1581, 1208, 1102, 1068, 839, 756 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{15}H_{18}OBr$ (MH^+): 293.05355; found: 293.05226; **HPLC** (Chiralcel OD-H; 1%/ 99% isopropanol/ hexanes, 0.5 mL/min; tr = 8.7 min (major), 9.4 min (minor); 97:3 er); $[\alpha]^{25}_{D}$ = –27.2° (c = 1.0, CH_2Cl_2). The absolute configuration for this product was assigned in analogy to that determined for product **2.22c**.

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Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                         Location :   36
Injection Date  : 10/26/2018 6:39:50 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-10-26 18-07-00\column3 1% IPA 99% hex 30min-0.5ml
                  .M (Sequence Method)
Last changed    : 10/26/2018 6:07:03 PM by SYSTEM
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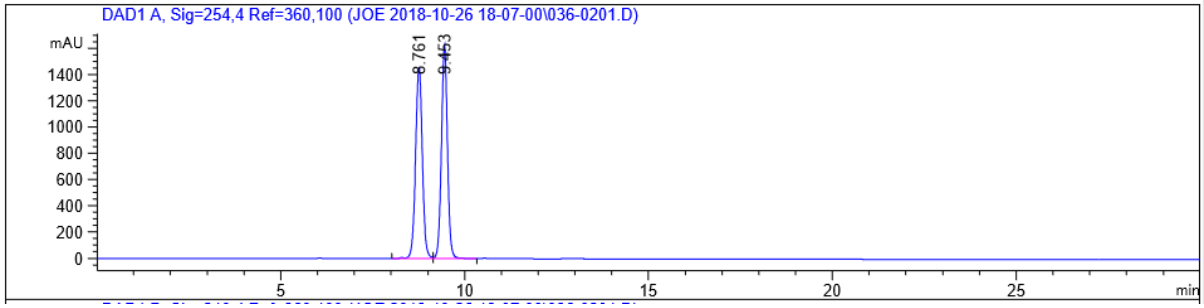
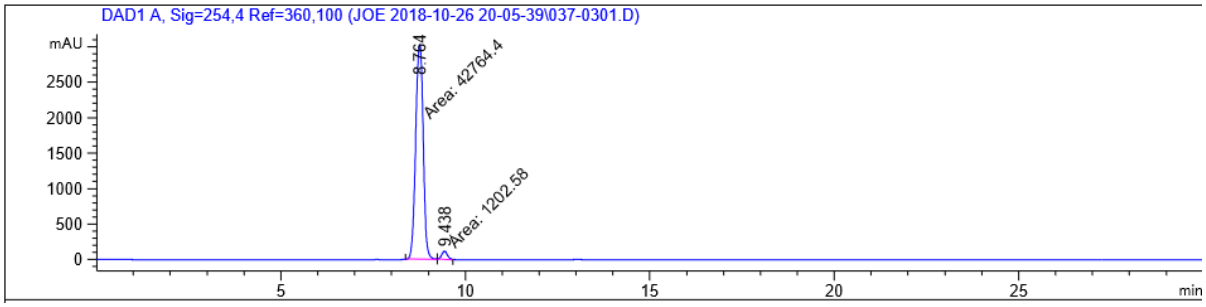


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

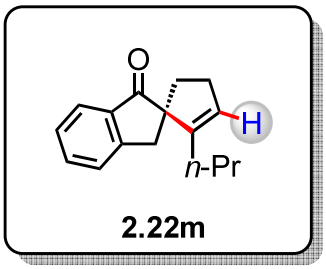
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.761	VV R	0.1948	1.86652e4	1457.95239	49.8964
2	9.453	VB	0.1758	1.87427e4	1634.13538	50.1036
Totals :				3.74079e4	3092.08777	

```
Acq. Operator   : SYSTEM                          Seq. Line :   3
Acq. Instrument : Wasa_LC1                         Location :   37
Injection Date  : 10/26/2018 9:09:24 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-10-26 20-05-39\column3 1% IPA 99% hex 30min-0.5ml
                  .M (Sequence Method)
Last changed    : 10/26/2018 8:05:41 PM by SYSTEM
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.764	MM	0.2357	4.27644e4	3023.44922	97.2648
2	9.438	MM	0.1751	1202.58374	114.45716	2.7352
Totals :				4.39669e4	3137.90638	

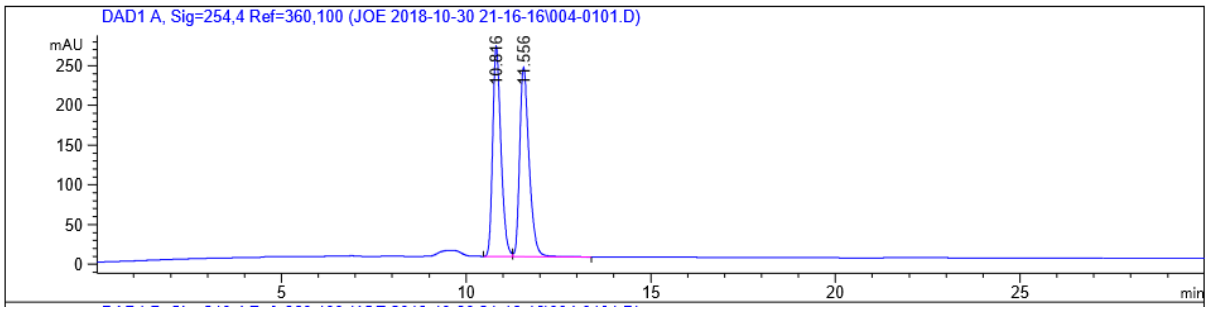


2.22m

(*R*)-2-Propylspiro[cyclopentane-1,2'-inden]-2-en-1'(3'*H*)-one (2.22m)

According to the General Procedure **C**, 2-(hept-3-yn-1-yl)-2,3-dihydro-1*H*-inden-1-one **2.21m** (45.3 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using *N*-methylpiperidine as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % EtOAc in hexanes) to give **2.22m** (44.4 mg, 98%) as a pale yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 1H), 5.70 – 5.63 (m, 1H), 3.24 (d, *J* = 17.4 Hz, 1H), 3.08 (d, *J* = 17.4 Hz, 1H), 2.58 – 2.50 (m, 1H), 2.50 – 2.35 (m, 2H), 1.95 – 1.85 (m, 1H), 1.73 – 1.64 (m, 2H), 1.51 – 1.32 (m, 2H), 0.82 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 213.24, 155.99, 148.63, 139.37, 137.47, 130.05, 129.49, 129.00, 126.73, 67.30, 42.38, 40.60, 33.51, 32.29, 23.50, 16.72; **IR** (neat) 2953, 2926, 2868, 2847, 1704, 1604, 1462, 1275, 909, 780, 729 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{16}H_{19}O$ (MH^+): 227.1430; found: 227.1429; **HPLC** (Chiralcel OD-H; 1%/ 99% isopropanol/ hexanes, 0.5 mL/min; tr = 10.7 min (minor), 11.5 min (major); 99:1 er); $[\alpha]^{25}_{D}$ = –131.7° (c = 1.0, CH_2Cl_2). The absolute configuration for this product was assigned in analogy to that determined for product **2.22c**.

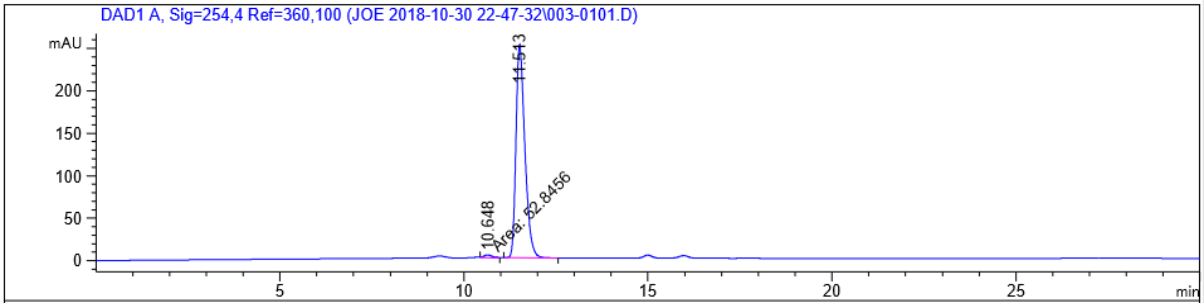
```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Wasa_LC1                         Location :   4
Injection Date  : 10/30/2018 9:18:10 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-10-30 21-16-16\column4 1%IPA 99% hexane 30min-0.
                  5mL.M (Sequence Method)
Last changed    : 10/30/2018 9:16:19 PM by SYSTEM
Method Info     : Column4 30min-1% iPrOH 99% hexane-0.5mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

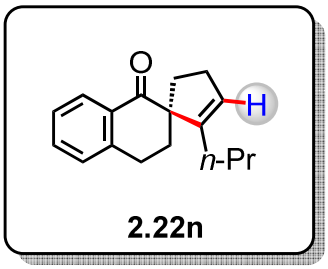
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.816	BV	0.2395	4120.73535	264.92889	49.4271
2	11.556	VB	0.2704	4216.26660	238.31940	50.5729
Totals :				8337.00195	503.24829	

```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Wasa_LC1                         Location :   3
Injection Date  : 10/30/2018 10:48:36 PM               Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-10-30 22-47-32\column4 1%IPA 99% hexane 30min-0.
                  5mL.M (Sequence Method)
Last changed    : 10/30/2018 10:47:34 PM by SYSTEM
Method Info     : Column4 30min-1% iPrOH 99% hexane-0.5mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.648	MM	0.2672	52.84563	3.29596	1.2355
2	11.513	BB	0.2582	4224.57324	251.23273	98.7645
Totals :				4277.41888	254.52868	



2.22n

(*R*)-2-Propyl-3',4'-dihydro-1'*H*-spiro[cyclopentane-1,2'-naphthalen]-2-en-1'-one (2.22n)

According to the General Procedure **D**, 2-(hept-3-yn-1-yl)-3,4-dihydronaphthalen-1(2*H*)-one **2.21n** (48.1 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using *N*-methylpiperidine as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % EtOAc in hexanes) to give **2.22n** (9.6 mg, 20%) as a pale yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 5.65 (s, 1H), 3.24 – 3.08 (m, 1H), 2.98 – 2.86 (m, 1H), 2.45 – 2.36 (m, 1H), 2.35 (dd, *J* = 4.4, 2.4 Hz, 2H), 2.05 (t, *J* = 6.9 Hz, 2H), 1.96 – 1.81 (m, 3H), 1.61 – 1.45 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 203.22, 149.39, 146.32, 135.73, 134.68, 131.15, 130.64, 129.28, 128.58, 64.11, 36.59, 35.00, 32.80, 32.37, 29.02, 23.72, 16.92; **IR** (neat) 2952, 2924, 2867, 2848, 1674, 1597, 1431, 1215, 904, 831, 789 cm^{-1}; HRMS (DART) m/z Calcd for $C_{17}H_{21}O$ (MH^+): 241.15869; found: 241.15884; **HPLC** (Chiralcel OD-H; 1%/ 99% isopropanol/ hexanes, 0.5 mL/min; tr = 10.0 min (major), 15.7 min (minor); 98:2 er); $[\alpha]^{25}_{D} = -12.3°$ (c = 1.0, CH_2Cl_2). The absolute configuration for this product was assigned in analogy to that determined for product **2.22c**.

```
Acq. Operator   : SYSTEM                          Seq. Line :   8
Acq. Instrument : Wasa_LC1                         Location :   83
Injection Date  : 11/24/2018 5:04:10 AM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-23 22-36-22\column3 1% IPA 99% hex 30min-0.5ml
                  .M (Sequence Method)
Last changed    : 11/23/2018 10:36:26 PM by SYSTEM
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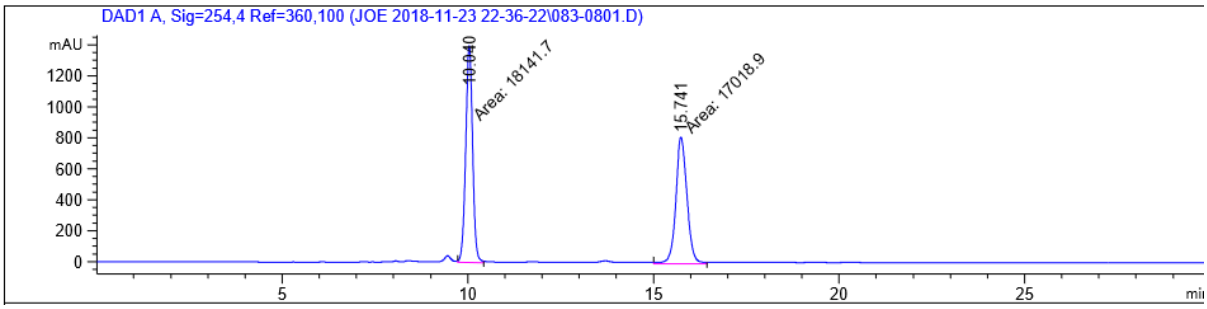

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.040	MM	0.2158	1.81417e4	1400.84106	51.5967
2	15.741	MM	0.3471	1.70189e4	817.21051	48.4033
Totals :				3.51607e4	2218.05157	

```
Acq. Operator   : SYSTEM                          Seq. Line :   9
Acq. Instrument : Wasa_LC1                         Location :   84
Injection Date  : 11/24/2018 5:35:06 AM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-23 22-36-22\column3 1% IPA 99% hex 30min-0.5ml
                  .M (Sequence Method)
Last changed    : 11/23/2018 10:36:26 PM by SYSTEM
Additional Info : Peak(s) manually integrated
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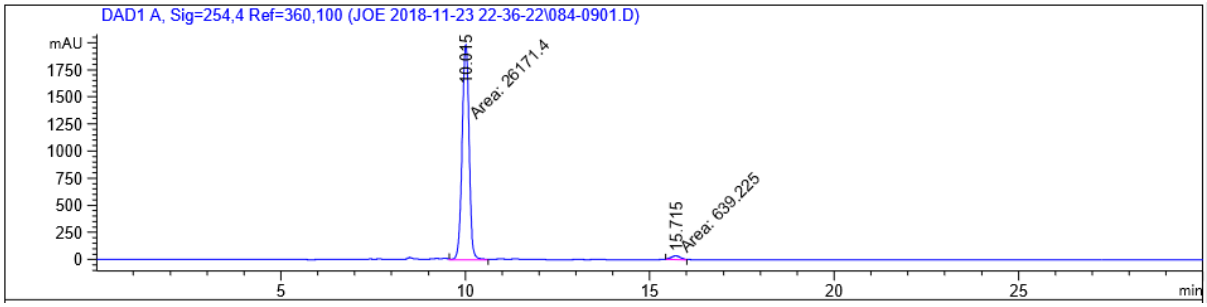
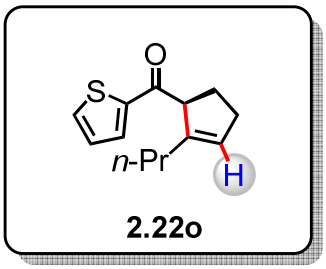


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.015	MM	0.2197	2.61714e4	1985.49268	97.6158
2	15.715	MM	0.3074	639.22522	34.66180	2.3842
Totals :				2.68107e4	2020.15448	



2.22o

(*S*)-(2-Propylcyclopent-2-en-1-yl)(thiophen-2-yl)methanone (2.22o)

According to the General Procedure **C**, 1-(thiophen-2-yl)non-5-yn-1-one **2.21o** (44.1 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using PMP as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % EtOAc in hexanes) to give **2.22o** (43.7 mg, 99%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.64 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.14 (dd, *J* = 4.9, 3.8 Hz, 1H), 5.64 (d, *J* = 1.6 Hz, 1H), 4.24 (t, *J* = 6.8 Hz, 1H), 2.58 – 2.47 (m, 1H), 2.45 – 2.36 (m, 1H), 2.36 – 2.27 (m, 1H), 2.18 – 2.09 (m, 1H), 2.09 – 2.00 (m, 1H), 2.00 – 1.91 (m, 1H), 1.54 – 1.36 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 195.69, 144.56, 143.01, 133.68, 131.99, 128.11, 127.68, 56.75, 32.04, 31.79, 29.77, 20.87, 13.96; **IR** (neat) 2953, 2926, 2866, 1652, 1410, 1231,1207, 1060, 892, 860, 720 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{13}H_{17}OS$ (MH^+): 221.0995; found: 221.0998; **HPLC** (Chiralcel OD-H; 1%/ 99% isopropanol/ hexanes, 0.5 mL/min; tr = 12.8 min (major), 14.8 min (minor); 98:2 er); $[\alpha]^{25}_D$ = –89.5° (c = 1.0, CH_2Cl_2). The absolute configuration for this product was assigned in analogy to that determined for product **2.22c**.

```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Wasa_LC1                         Location :   33
Injection Date  : 10/26/2018 6:08:53 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2018-10-26 18-07-00\column3 1% IPA 99% hex 30min-0.5ml
                  .M
Last changed    : 10/26/2018 6:07:03 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2018-10-26 18-07-00\column3 1% IPA 99% hex 30min-0.5ml
                  .M (Sequence Method)
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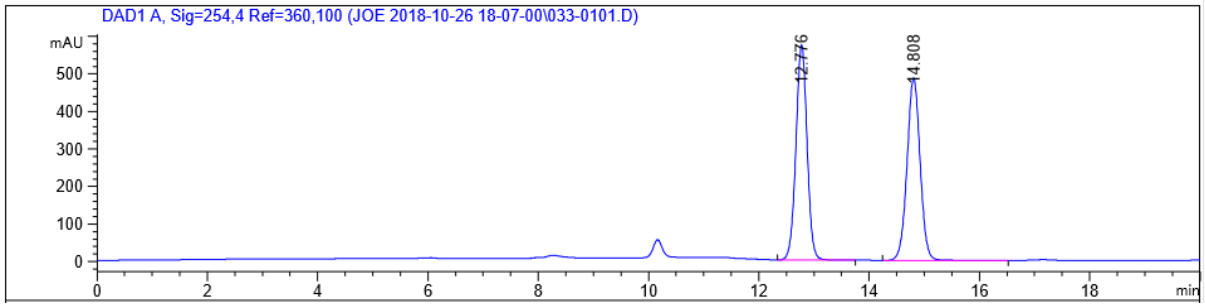

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.776	BB	0.2154	8034.31201	573.58746	50.0399
2	14.808	BB	0.2545	8021.49268	486.06281	49.9601
Totals :				1.60558e4	1059.65027	

```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Wasa_LC1                         Location :   2
Injection Date  : 11/2/2018 11:22:22 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-02 23-20-33\column3 1%IPA 99% hexane 20min-0.
                  5mL.M (Sequence Method)
Last changed    : 11/2/2018 11:20:36 PM by SYSTEM
Method Info     : Column3 20min-1% iPrOH 99% hexane-0.5mL
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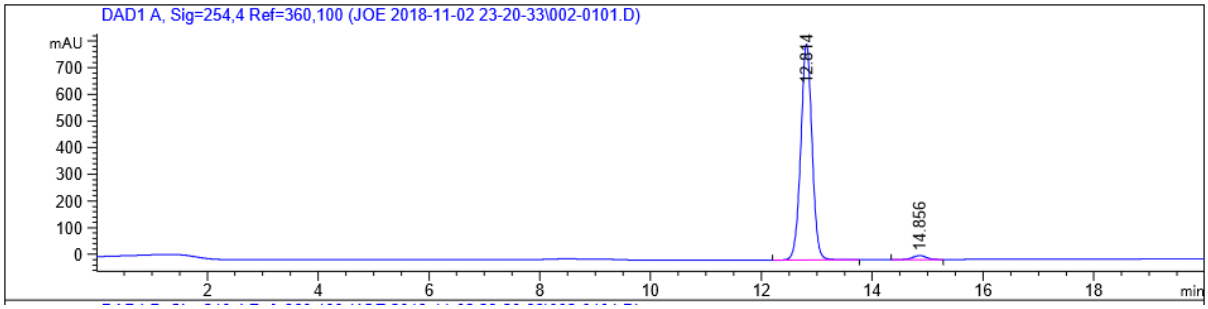
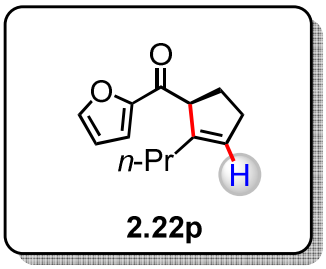


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.814	BB	0.2167	1.14259e4	809.15973	97.8943
2	14.856	BB	0.2528	245.76530	15.02457	2.1057
Totals :				1.16717e4	824.18430	



2.22p

(*S*)-Furan-2-yl(2-propylcyclopent-2-en-1-yl)methanone (2.22p)

According to the General Procedure **C**, 1-(furan-2-yl)non-5-yn-1-one **2.21p** (40.9 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using PMP as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % EtOAc in hexanes) to give **2.22p** (40.5 mg, 99%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.23 (dd, *J* = 3.5, 0.8 Hz, 1H), 6.55 (dd, *J* = 3.6, 1.7 Hz, 1H), 5.63 (d, *J* = 1.7 Hz, 1H), 4.26 – 4.18 (m, 1H), 2.57 – 2.46 (m, 1H), 2.43 – 2.34 (m, 1H), 2.33 – 2.22 (m, 1H), 2.16 – 2.07 (m, 1H), 2.07 – 1.98 (m, 1H), 1.98 – 1.88 (m, 1H), 1.53 – 1.35 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 191.79, 152.78, 146.52, 142.82, 127.68, 117.54, 112.16, 55.47, 31.98, 31.72, 29.18, 20.83, 13.93; **IR** (neat) 2955, 2928, 1662, 1564, 1462, 1390, 1289, 1013, 811, 918, 593 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{13}H_{17}O_2$ (MH^+): 205.1223; found: 205.1218; **HPLC** (Chiralcel OD-H; 1%/ 99% isopropanol/ hexanes, 0.5 mL/min; tr = 12.3 min (major), 15.7 min (minor); 97:3 er); $[\alpha]^{25}_D = -103.8°$ (c = 1.0, CH_2Cl_2). The absolute configuration for this product was assigned in analogy to that determined for product **2.22c**.

```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                         Location :   81
Injection Date  : 11/1/2018 12:42:30 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-01 12-09-36\column3 1% IPA 99% hex 30min-0.5ml
                  .M (Sequence Method)
Last changed    : 11/1/2018 12:09:40 PM by SYSTEM
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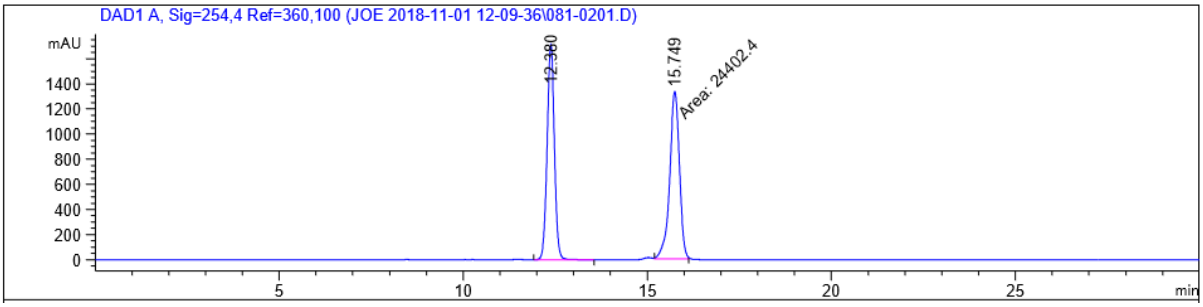

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.380	BB	0.2139	2.34575e4	1711.65735	49.0128
2	15.749	MM	0.3058	2.44024e4	1329.98621	50.9872
Totals :				4.78598e4	3041.64355	

```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Wasa_LC1                         Location :   5
Injection Date  : 11/6/2018 11:42:51 AM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-06 11-40-57\column3 1%IPA 99% hexane 20min-0.
                  5mL.M (Sequence Method)
Last changed    : 11/6/2018 11:41:01 AM by SYSTEM
Method Info     : Column3 20min-1% iPrOH 99% hexane-0.5mL
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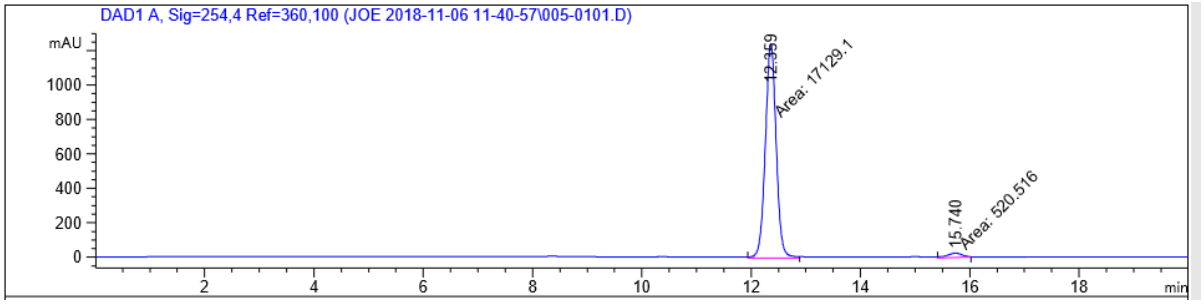
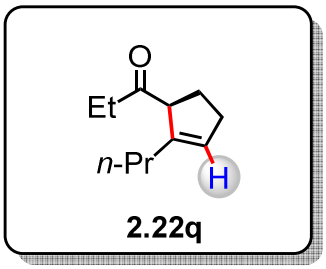


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.359	MM	0.2297	1.71291e4	1243.10815	97.0508
2	15.740	MM	0.3304	520.51581	26.25672	2.9492
Totals :				1.76496e4	1269.36487	



(*S*)-1-(2-Propylcyclopent-2-en-1-yl)propan-1-one (2.22q)

According to the General Procedure **C**, undec-7-yn-3-one **2.21q** (33.2 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using PMP as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % Et_2O in pentane) to give **2.22q** (30.2 mg, 91%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.58 (s, 1H), 3.51 (t, J = 9.0 Hz, 1H), 2.45 (q, J = 7.1 Hz, 3H), 2.41 – 2.30 (m, 1H), 2.20 – 2.10 (m, 1H), 2.04 – 1.87 (m, 3H), 1.54 – 1.36 (m, 2H), 1.05 (t, J = 7.3 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 216.66, 145.66, 130.17, 63.15, 36.08, 34.70, 34.43, 30.72, 23.45, 16.61, 10.52; **IR** (neat) 2955, 2924,2869, 2850, 1704, 1457, 1376, 1181, 1111, 798 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{11}H_{19}O$ (MH^+): 167.14304; found: 167.14224; **HPLC** (Chiralcel OD-H; 0.3%/ 99.7% isopropanol/ hexanes, 0.5 mL/min; tr = 13.9 min (major), 14.7 min (minor); 95:5 er); $[\alpha]^{25}_{D}$ = –189.3° (c = 1.0, CH_2Cl_2). The absolute configuration for this product was assigned in analogy to that determined for product **2.22c**.

```
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Wasa_LC1                         Location :   9
Injection Date  : 11/20/2018 4:48:54 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-20 16-47-45\column3 0.3% IPA 99.7% hex 30min-0
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Last changed    : 11/20/2018 4:47:48 PM by SYSTEM
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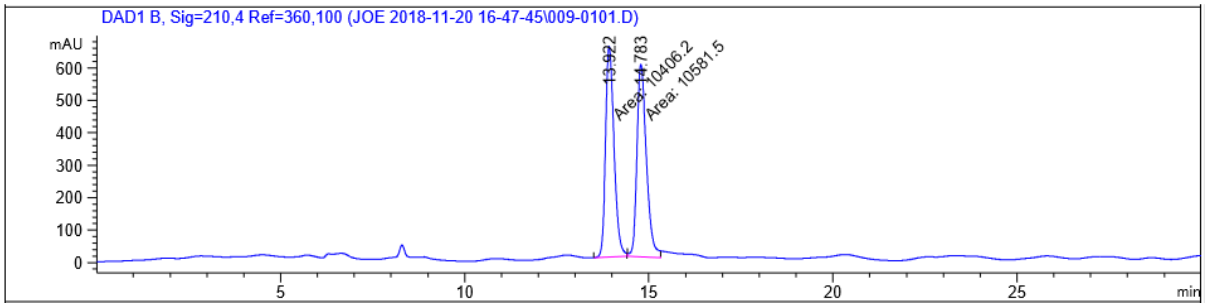

Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.922	MM	0.2668	1.04062e4	649.97485	49.5824
2	14.783	MM	0.2971	1.05815e4	593.56140	50.4176
Totals :				2.09877e4	1243.53625	

```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                         Location :   8
Injection Date  : 11/20/2018 5:19:50 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-20 16-47-45\column3 0.3% IPA 99.7% hex 30min-0
                  .5ml.M (Sequence Method)
Last changed    : 11/20/2018 4:47:48 PM by SYSTEM
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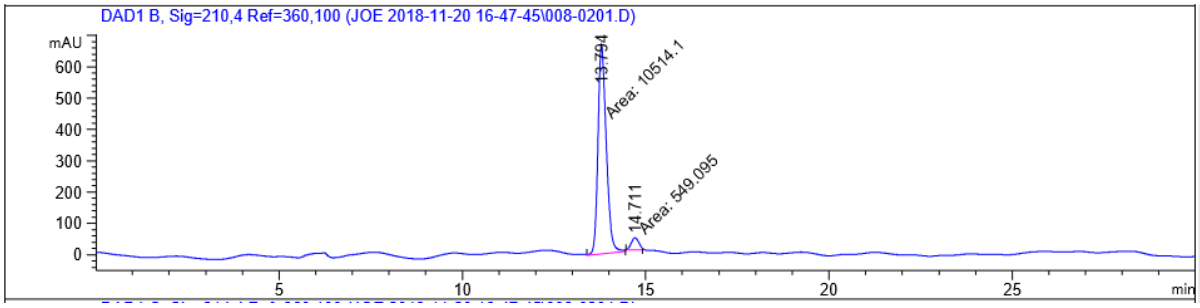
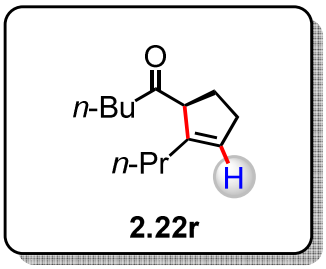


Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.794	MM	0.2625	1.05141e4	667.44690	95.0367
2	14.711	MM	0.2392	549.09467	38.26130	4.9633
Totals :				1.10632e4	705.70820	



2.22r

(*S*)-1-(2-Propylcyclopent-2-en-1-yl)pentan-1-one (2.22r)

According to the General Procedure **C**, tridec-9-yn-5-one **2.21r** (38.9 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using PMP as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % Et_2O in pentane) to give **2.22r** (30.3 mg, 78%) as a colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.61 – 5.55 (m, 1H), 3.49 (d, J = 5.8 Hz, 1H), 2.51 – 2.40 (m, 3H), 2.40 – 2.32 (m, 1H), 2.19 – 2.09 (m, 1H), 2.04 – 1.87 (m, 3H), 1.58 – 1.52 (m, 2H), 1.52 – 1.37 (m, 2H), 1.30 (h, J = 7.4 Hz, 2H), 0.95 – 0.84 (m, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 216.22, 145.64, 130.19, 63.33, 42.69, 34.69, 34.43, 30.61, 28.47, 25.06, 23.45, 16.61, 16.54; **IR** (neat) 2954, 2928, 2869, 1703, 1461, 1405, 1377, 1125, 1060 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{13}H_{23}O$ (MH^+): 195.17434; found: 195.17326; **HPLC** (Chiralcel OD-H; 0.3%/ 99.7% isopropanol/ hexanes, 0.5 mL/min; tr = 14.4 min (major), 16.1 min (minor); 96:4 er); $[\alpha]^{25}_{D}$ = −136.9° (c = 1.0, CH_2Cl_2). The absolute configuration for this product was assigned in analogy to that determined for product **2.22c**.

```
Acq. Operator   : SYSTEM                          Seq. Line :   4
Acq. Instrument : Wasa_LC1                         Location :   81
Injection Date  : 12/1/2018 10:26:02 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-12-01 19-21-25\column3 0.3% IPA 99.7% hex 60min-0
                  .5ml.M (Sequence Method)
Last changed    : 12/1/2018 7:21:28 PM by SYSTEM
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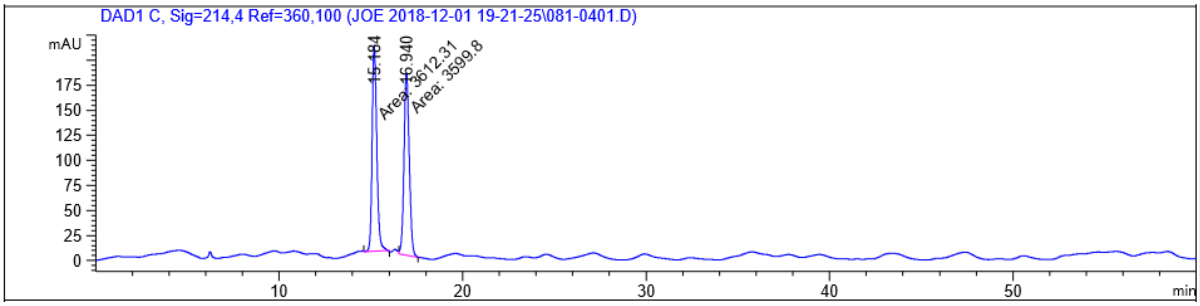

Signal 3: DAD1 C, Sig=214,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.184	MM	0.2931	3612.30859	205.42609	50.0867
2	16.940	MM	0.3289	3599.79712	182.43704	49.9133
Totals :				7212.10571	387.86313	

```
Acq. Operator   : SYSTEM                          Seq. Line :   6
Acq. Instrument : Wasa_LC1                         Location :   84
Injection Date  : 12/2/2018 12:27:54 AM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-12-01 19-21-25\column3 0.3% IPA 99.7% hex 60min-0
                  .5ml.M (Sequence Method)
Last changed    : 12/1/2018 7:21:28 PM by SYSTEM
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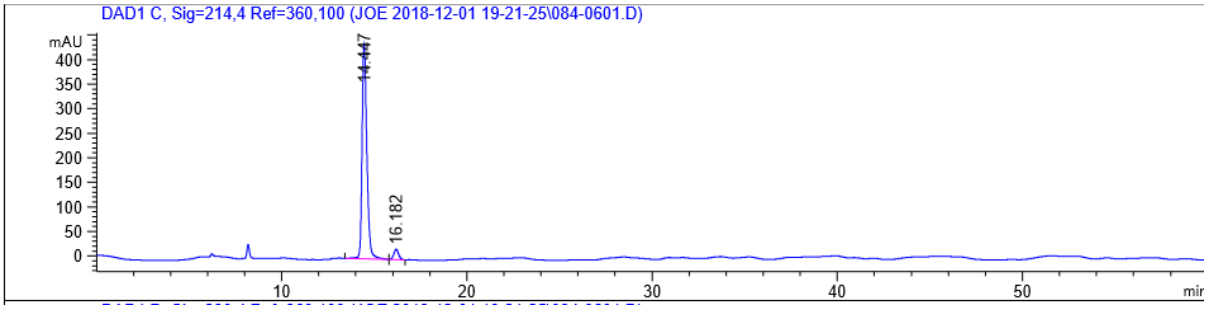
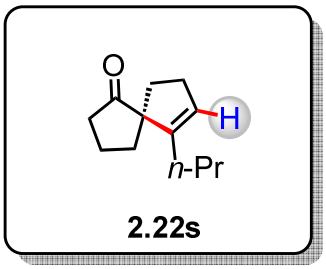


Signal 3: DAD1 C, Sig=214,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.447	BB	0.2709	7856.40430	438.82300	95.4427
2	16.182	BB	0.2758	375.13409	21.06031	4.5573
Totals :				8231.53839	459.88330	



2.22s

(*S*)-6-Propylspiro[4.4]non-6-en-1-one (2.22s)

According to the General Procedure **C**, 2-(hept-3-yn-1-yl)cyclopentan-1-one **2.21s** (35.7 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using *N*-methylpiperidine as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % Et_2O in pentane) to give **2.22s** (28.4 mg, 82%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.65 – 5.59 (m, 1H), 2.45 – 2.26 (m, 3H), 2.23 – 2.10 (m, 1H), 2.10 – 2.00 (m, 3H), 1.91 – 1.78 (m, 4H), 1.78 – 1.71 (m, 1H), 1.58 – 1.38 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 222.72, 145.09, 126.90, 64.61, 38.05, 36.91, 34.51, 30.14, 20.93, 20.06, 14.15; **IR** (neat) 2953, 2924, 2867, 1730, 1449, 1121, 1092, 959, 890, 817, 790 cm^{-1}; **HRMS** (DART) m/z Calcd for $C_{12}H_{19}O$ (MH^+): 179.14304; found: 179.14233; HPLC (Chiralcel OJ-H; 0.5%/ 99.5% isopropanol/ hexanes, 0.5 mL/min; tr = 9.2 min (major), 9.7 min (minor); 80:20 er); $[\alpha]^{25}_{D}$ = –42.5° (c = 1.0, CH_2Cl_2). The absolute configuration for this product was assigned in analogy to that determined for product **2.22c**.

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Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                         Location :   81
Injection Date  : 11/8/2018 3:54:09 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-08 15-32-10\column4 0.5%IPA 99.5% hexane 20min
                  -0.5mL.M (Sequence Method)
Last changed    : 11/8/2018 3:32:13 PM by SYSTEM
Method Info     : Column4 20min-0.5% iPrOH 99.5% hexane-0.5mL
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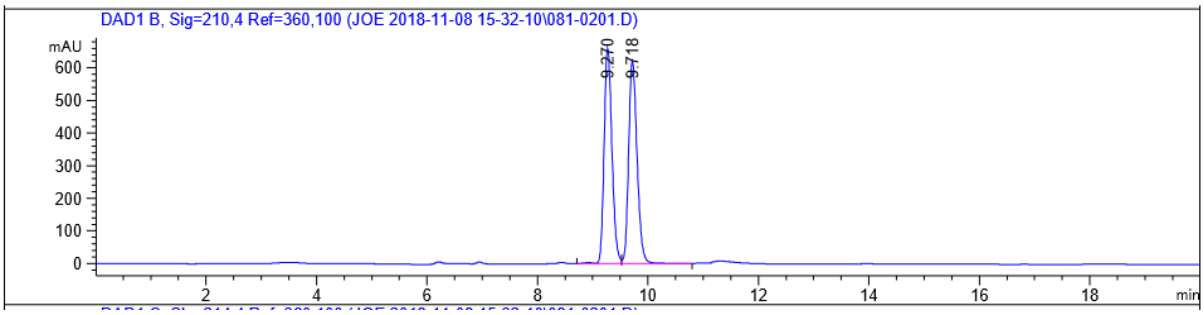

Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.270	VV R	0.1523	6506.55078	660.50195	49.5610
2	9.718	VB	0.1663	6621.80811	621.45270	50.4390
Totals :				1.31284e4	1281.95465	

```
Acq. Operator   : SYSTEM                          Seq. Line :   3
Acq. Instrument : Wasa_LC1                         Location :   82
Injection Date  : 11/8/2018 4:15:05 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-11-08 15-32-10\column4 0.5%IPA 99.5% hexane 20min
                  -0.5mL.M (Sequence Method)
Last changed    : 11/8/2018 3:32:13 PM by SYSTEM
Method Info     : Column4 20min-0.5% iPrOH 99.5% hexane-0.5mL
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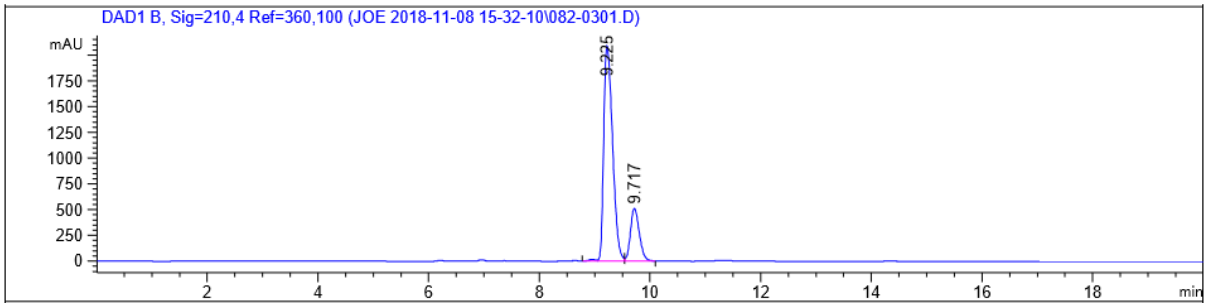
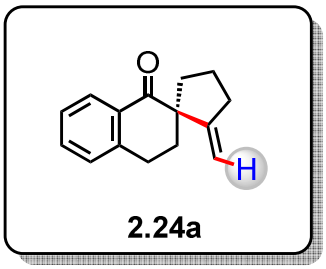


Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.225	VV R	0.1751	2.32191e4	2087.54468	80.4174
2	9.717	VB	0.1734	5654.11865	509.70819	19.5826
Totals :				2.88732e4	2597.25287	



(*R*)-2-Methylene-3',4'-dihydro-1'*H*-spiro[cyclopentane-1,2'-naphthalen]-1'-one (2.24a)

According to the General Procedure **C**, 2-(pent-4-yn-1-yl)-3,4-dihydronaphthalen-1(2*H*)-one[20i] **2.23a** (42.5 mg, 0.2 mmol) was subjected to the Conia-ene-type reaction using *N*-methylpiperidine as the Brønsted base catalyst. The product was purified by silica gel column chromatography (1.0 % EtOAc in hexanes) to give **2.24a** (41.6 mg, 98%) as a pale yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 5.01 (s, 1H), 4.65 (s, 1H), 3.12 – 3.01 (m, 1H), 3.01 – 2.91 (m, 1H), 2.67 – 2.54 (m, 1H), 2.53 – 2.43 (m, 1H), 2.41 – 2.29 (m, 1H), 2.29 – 2.18 (m, 1H), 2.04 – 1.90 (m, 1H), 1.87 – 1.76 (m, 1H), 1.76 – 1.65 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 203.13, 157.96, 146.40, 135.75, 134.78, 131.32, 130.73, 129.27, 109.75, 59.45, 39.27, 36.77, 36.63, 28.87, 25.51; **IR** (neat) 2829, 2874, 1677, 1598, 1452, 1430, 1317, 1218, 889, 740 cm^{-1}; **HRMS** (DART) Calcd for $C_{15}H_{17}O$ (MH^+): 213.12739; found: 213.12739; **HPLC** (Chiralcel OJ-H; 1%/ 99% isopropanol/ hexanes, 0.5 mL/min; tr = 15.6 min (major), 17.6 min (minor); 68:32 er); $[\alpha]^{25}_D$ = +4.0° (c = 1.0, CH_2Cl_2). The absolute configuration for this product was assigned in analogy to that determined for product **2.22c**.

```
Acq. Operator   : SYSTEM                          Seq. Line :   3
Acq. Instrument : Wasa_LC1                         Location :   51
Injection Date  : 12/4/2018 9:08:48 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-12-04 19-05-00\column4 1%IPA 99% hexane 30min-0.
                  5mL.M (Sequence Method)
Last changed    : 12/4/2018 7:05:03 PM by SYSTEM
Method Info     : Column4 30min-1% iPrOH 99% hexane-0.5mL
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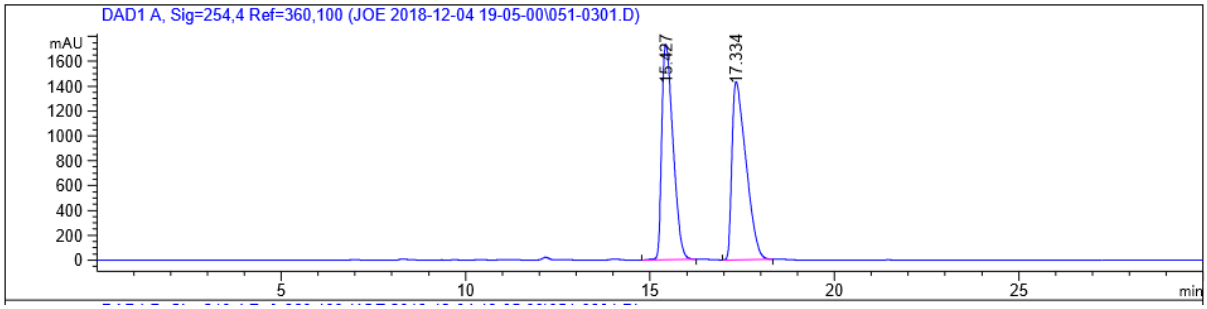

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.427	BB	0.3329	3.66785e4	1733.05493	49.2144
2	17.334	BB	0.4060	3.78495e4	1433.69092	50.7856
Totals :				7.45279e4	3166.74585	

```
Acq. Operator   : SYSTEM                          Seq. Line :   4
Acq. Instrument : Wasa_LC1                         Location :   52
Injection Date  : 12/4/2018 9:39:44 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2018-12-04 19-05-00\column4 1%IPA 99% hexane 30min-0.
                  5mL.M (Sequence Method)
Last changed    : 12/4/2018 7:05:03 PM by SYSTEM
Method Info     : Column4 30min-1% iPrOH 99% hexane-0.5mL
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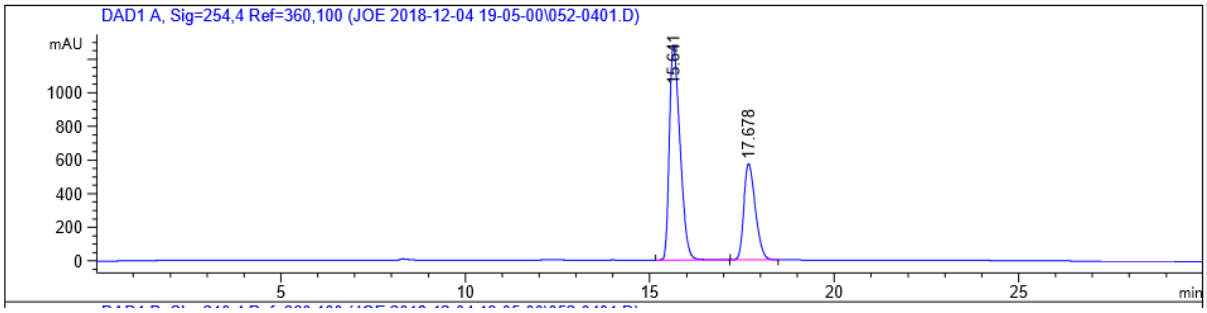
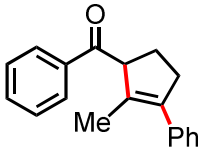


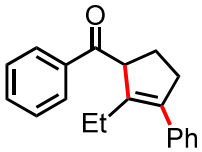
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.641	BB	0.3119	2.56366e4	1278.67749	67.4907
2	17.678	BB	0.3360	1.23488e4	571.76593	32.5093
Totals :				3.79854e4	1850.44342	



(2-methyl-3-phenylcyclopent-2-en-1-yl)(phenyl)methanone (2.28a)

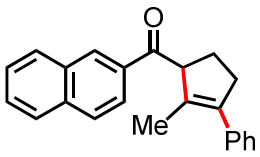
According to the General Procedure **E**, 1-phenylnon-5-yn-1-one **2.21a** (18.6 mg, 0.10 mmol) reacted with iodobenzene **2.27a** (24.5 mg, 0.12 mmol**)** following the general procedure. After purification by column chromatography (Hexane:Ethyl acetate = 40:1), **2.28a** was obtained as a colorless liquid (24.9 mg, 95%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.4 Hz, 2H), 7.57 (t, J = 7.3 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.40 – 7.32 (m, 4H), 7.28 – 7.21 (m, 1H), 4.63 – 4.56 (m, 1H), 2.86 (t, *J* = 6.4 Hz, 2H), 2.45 – 2.33 (m, 1H), 2.16 – 2.03 (m, 1H), 1.80 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) 202.2, 139.1, 137.9, 137.2, 133.1, 133.0, 128.7, 128.6, 128.1, 127.9, 126.7, 77.3, 77.0, 76.8, 58.9, 36.4, 27.7, 14.9; **IR** (neat) 1717, 1674, 1176, 1157, 850, 760, 695 cm^{-1}; HRMS (DART) m/z Calcd for $C_{19}H_{19}O$ (MH^+): 263.1430; found: 263.1439.



(2-ethyl-3-phenylcyclopent-2-en-1-yl)(phenyl)methanone (2.28b)

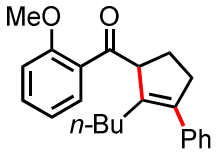
According to the General Procedure **E**, 1-phenyloct-5-yn-1-one **2.21d** (20.0 mg, 0.10 mmol) reacted with iodobenzene **2.27a** (24.5 mg, 0.12 mmol**)** following the general procedure. After purification by column chromatography (Hexane:Ethyl acetate = 40:1), **2.28b** was obtained as a colorless liquid (27.5 mg, 98%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 – 7.92 (m, 2H), 7.49 (t, *J* = 6.7 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.31 – 7.21 (m, 4H), 7.16 (t, *J* = 6.9 Hz, 1H), 4.67 – 4.58 (m, 1H), 2.85 – 2.77 (m, 1H), 2.71 (dd, *J* = 16.7, 7.2 Hz, 1H), 2.43 – 2.23 (m, 3H), 2.09 – 1.90 (m, 2H), 0.84 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.33, 139.04, 139.01, 138.06,

137.07, 132.94, 128.64, 128.45, 128.06, 127.82, 126.65, 55.45, 36.73, 28.12, 21.21, 12.87; **IR** (neat) 2961, 1677, 1595, 1208, 1177, 761, 698 cm^{-1}; HRMS (DART) m/z Calcd for $C_{20}H_{21}O$ (MH^+): 277.1587; found: 277.1586.



(2-methyl-3-phenylcyclopent-2-en-1-yl)(naphthalen-2-yl)methanone (2.28c)

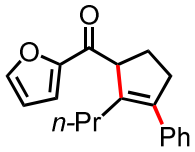
According to the General Procedure **E**, 1-(naphthalen-2-yl)hept-5-yn-1-one **2.21u** (23.6 mg, 0.10 mmol) reacted with iodobenzene **2.27a** (24.5 mg, 0.12 mmol**)** following the general procedure. After purification by column chromatography (Hexane:Ethyl acetate = 40:1), **2.28c** was obtained as a yellow solid (28.5 mg, 91%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.82 (dd, *J* = 13.2, 8.4 Hz, 2H), 7.50 (dt, *J* = 19.7, 7.0 Hz, 2H), 7.28 (d, *J* = 4.4 Hz, 4H), 7.17 (dd, *J* = 7.8, 3.5 Hz, 1H), 4.68 (t, *J* = 7.6 Hz, 1H), 2.90 – 2.72 (m, 2H), 2.47 – 2.28 (m, 1H), 2.10 (dq, *J* = 13.6, 6.9 Hz, 1H), 1.75 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.2, 139.1, 137.8, 135.5, 134.5, 133.2, 132.6, 130.2, 129.6, 128.5, 128.4, 128.1, 127.9, 127.7, 126.7, 126.6, 124.3, 58.9, 36.4, 27.8, 14.9; **IR** (neat) 1669, 1624, 1461, 1438, 1274, 697, 647 cm^{-1}; HRMS (DART) m/z Calcd for $C_{23}H_{21}O$ (MH^+): 313.1587; found: 313.1583.



(2-butyl-3-phenylcyclopent-2-en-1-yl)(2-methoxyphenyl)methanone (2.28d)

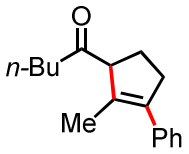
According to the General Procedure **E**, 1-(2-methoxyphenyl)dec-5-yn-1-one **2.21v** (25.8 mg, 0.10 mmol) reacted with iodobenzene **2.27a** (24.5 mg, 0.12 mmol**)** following the general procedure.

After purification by column chromatography (Hexane:Ethyl acetate = 40:1), **2.28d** was obtained as a white solid (25.1 mg, 75%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.8 Hz, 1H), 7.44 (t, *J* = 8.5 Hz, 1H), 7.31 (dt, *J* = 14.0, 7.3 Hz, 4H), 7.22 (t, *J* = 7.0 Hz, 1H), 7.07 – 6.89 (m, 2H), 4.76 – 4.61 (m, 1H), 3.90 (s, 3H), 2.87 – 2.75 (m, 1H), 2.75 – 2.62 (m, 1H), 2.42 – 2.16 (m, 2H), 2.09 (dd, *J* = 13.3, 8.5 Hz, 2H), 1.44 – 1.05 (m, 4H), 0.76 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.96, 157.91, 139.21, 138.39, 138.38, 132.78, 129.88, 129.78, 127.96, 127.86, 126.42, 120.67, 111.40, 59.94, 55.46, 36.55, 30.25, 27.87, 27.62, 22.69, 13.81; **IR** (neat) 2953, 1670, 1193, 1179, 906, 754, 727 cm^{-1}; HRMS (DART) m/z Calcd for $C_{23}H_{27}O_2$ (MH^+): 335.2006; found: 335.2012.



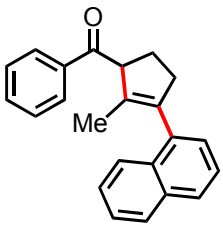
furan-2-yl(3-phenyl-2-propylcyclopent-2-en-1-yl)methanone (2.28e)

According to the General Procedure **E**, 1-(furan-2-yl)non-5-yn-1-one **2.21q** (20.4 mg, 0.10 mmol) reacted with iodobenzene **2.27a** (24.5 mg, 0.12 mmol**)** following the general procedure. After purification by column chromatography (Hexane:Ethyl acetate = 40:1), **2.28e** was obtained as a colorless liquid (18.3 mg, 65%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.28 – 7.21 (m, 2H), 6.56 (s, 1H), 4.48 (dd, *J* = 9.1, 6.5 Hz, 1H), 2.95 – 2.85 (m, 1H), 2.85 – 2.76 (m, 1H), 2.37 – 2.26 (m, 2H), 2.17 – 2.08 (m, 1H), 2.02 (t, *J* = 9.4 Hz, 1H), 1.53 – 1.37 (m, 1H), 1.34 – 1.21 (m, 1H), 0.79 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 191.6, 152.7, 146.5, 140.1, 138.1, 137.2, 128.1, 127.8, 126.7, 117.5, 112.2, 56.5, 37.0, 30.1, 27.7, 21.4, 14.1; **IR** (neat) 3118, 1970, 1718, 1491, 1463, 1084, 834, 802 cm^{-1}; HRMS (DART) m/z Calcd for $C_{19}H_{21}O_2$ (MH^+): 281.1536; found: 281.1535.



1-(2-methyl-3-phenylcyclopent-2-en-1-yl)pentan-1-one (2.28f)

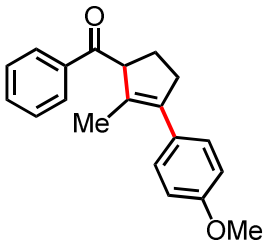
According to the General Procedure **E**, undec-9-yn-5-one **2.21x** (16.6 mg, 0.10 mmol) reacted with iodobenzene **2.27a** (24.5 mg, 0.12 mmol**)** following the general procedure. After purification by column chromatography (Hexane:Ethyl acetate = 40:1), **2.28f** was obtained as a colorless liquid (22.1 mg, 91%). **^{1}H NMR** (500 MHz, $CDCl_3$) 7.35 (t, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 7.0 Hz, 2H), 7.25 (d, *J* = 7.1 Hz, 1H), 3.72 – 3.59 (m, 1H), 2.91 – 2.72 (m, 2H), 2.47 (td, *J* = 17.0, 16.4, 7.5 Hz, 2H), 2.22 (dd, *J* = 13.3, 6.3 Hz, 1H), 1.99 (dd, *J* = 13.4, 8.5 Hz, 1H), 1.78 (s, 3H), 1.59 (p, *J* = 7.2 Hz, 2H), 1.32 (h, *J* = 7.3 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) 213.1, 139.4, 137.7, 132.7, 128.1, 127.8, 126.8, 64.7, 40.2, 36.5, 26.0, 25.8, 22.4, 14.6, 13.9; **IR** (neat) 2955, 1699, 1621, 1261, 1227, 762 cm^{-1}; HRMS (DART) m/z Calcd for $C_{17}H_{23}O$ (MH^+): 243.1743; found: 243.1739.



(2-methyl-3-(naphthalen-1-yl)cyclopent-2-en-1-yl)(phenyl)methanone (2.28g)

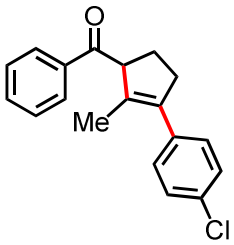
According to the General Procedure **E**, 1-phenylnon-5-yn-1-one **2.21a** (18.6 mg, 0.10 mmol) reacted with 1-iodonaphthalene **2.27b** (30.5 mg, 0.12 mmol**)** following the general procedure. After purification by column chromatography (Hexane:Ethyl acetate = 40:1), **2.28g** was obtained as a bright yellow solid (28.8 mg, 92%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.1 (d, *J* = 8.2 Hz, 3H), 7.9 (d, *J* = 8.1 Hz, 1H), 7.8 (d, *J* = 8.1 Hz, 1H), 7.6 (t, *J* = 7.9 Hz, 1H), 7.6 – 7.4 (m, 5H), 7.3 (d, *J*

= 6.8 Hz, 1H), 4.7 (dd, *J* = 10.3, 5.1 Hz, 1H), 2.9 (d, *J* = 9.0 Hz, 1H), 2.8 (s, 1H), 2.6 – 2.5 (m, 1H), 2.3 (dd, *J* = 8.8, 4.7 Hz, 1H), 1.5 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.2, 139.1, 137.1, 136.6, 134.9, 133.7, 133.0, 131.4, 128.7, 128.6, 128.2, 127.1, 126.1, 126.0, 125.7, 125.6, 125.4, 57.7, 38.6, 28.4, 14.4; **IR** (neat) 2921, 1676, 1594, 1320, 1252, 801, 777 cm^{-1}; HRMS (DART) m/z Calcd for $C_{23}H_{21}O$ (MH^+): 313.1587; found: 313.1591.



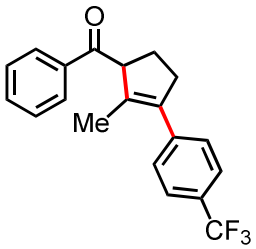
(3-(4-methoxyphenyl)-2-methylcyclopent-2-en-1-yl)(phenyl)methanone (2.28h)

According to the General Procedure **E**, 1-phenylnon-5-yn-1-one **2.21a** (18.6 mg, 0.10 mmol) reacted with 1-iodo-4-methoxybenzene **2.27c** (28.1 mg, 0.12 mmol**)** following the general procedure. After purification by column chromatography (Hexane:Ethyl acetate = 40:1), **2.28h** was obtained as a yellow solid (27.8 mg, 95%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.62 – 4.52 (m, 1H), 3.81 (s, 3H), 2.83 (t, *J* = 7.3 Hz, 2H), 2.44 – 2.29 (m, 1H), 2.14 – 2.01 (m, 1H), 1.79 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.3, 158.2, 138.4, 137.1, 132.9, 131.7, 130.3, 129.0, 128.6, 128.5, 113.5, 58.9, 55.2, 36.4, 27.6, 14.9; **IR** (neat) 2929, 1675, 1508, 1243, 1208, 1176, 829, 696 cm^{-1}; HRMS (DART) m/z Calcd for $C_{20}H_{21}O_2$ (MH^+): 293.1536; found: 293.1541.



(3-(4-chlorophenyl)-2-methylcyclopent-2-en-1-yl)(phenyl)methanone (2.28i)

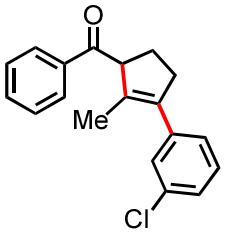
According to the General Procedure **E**, 1-phenylnon-5-yn-1-one **2.21a** (18.6 mg, 0.10 mmol) reacted with 1-chloro-4-iodobenzene **2.27d** (28.6 mg, 0.12 mmol**)** following the general procedure. After purification by column chromatography (Hexane:Ethyl acetate = 40:1), **2.28i** was obtained as a colorless liquid (27.6 mg, 93%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.3 Hz, 2H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.9 Hz, 2H), 4.59 (d, *J* = 15.7 Hz, 1H), 2.82 (t, *J* = 7.2 Hz, 2H), 2.47 – 2.31 (m, 1H), 2.10 (dq, *J* = 13.1, 6.3 Hz, 1H), 1.78 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.0, 138.0, 137.0, 136.2, 133.9, 133.1, 132.3, 129.2, 128.7, 128.5, 128.2, 58.7, 36.3, 27.7, 14.9; **IR** (neat) 2933, 1675, 1445, 1341, 1208, 1091, 826 cm^{-1}; HRMS (DART) m/z Calcd for $C_{19}H_{18}O_1Cl$ (MH^+): 297.1041; found: 297.1041.



(2-methyl-3-(4-(trifluoromethyl)phenyl)cyclopent-2-en-1-yl)(phenyl)methanone (2.28j)

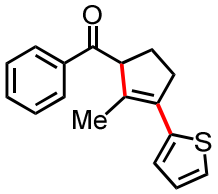
According to the General Procedure **E**, 1-phenylnon-5-yn-1-one **2.21a** (18.6 mg, 0.10 mmol) reacted with 1-iodo-4-(trifluoromethyl)benzene **2.27e** (32.7 mg, 0.12 mmol**)** following the general procedure. After purification by column chromatography (Hexane:Ethyl acetate = 40:1), **2.28j** was obtained as a colorless liquid (30.1mg, 91%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.4 Hz,

2H), 7.60 (t, J = 7.9 Hz, 3H), 7.50 (t, J = 7.8 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 4.68 – 4.57 (m, 1H), 2.95 – 2.76 (m, 2H), 2.48 – 2.36 (m, 1H), 2.17 – 2.05 (m, 1H), 1.81 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$ δ 201.77, 141.47, 141.46, 137.97, 136.94, 135.35, 133.15, 128.71, 128.55, 124.31 (q, J = 272.7 Hz), 125.06 (q, J = 3.8 Hz), 124.95, 58.71, 36.23, 27.74, 14.88; **^{19}F NMR** (564 MHz, $CDCl_3$) δ −62.44; **IR** (neat) 1677, 1322, 1163, 1067, 886, 697 cm^{-1}; HRMS (DART) m/z Calcd for $C_{20}H_{18}O_1F_3$ (MH^+): 331.1304; found: 331.1292.



(3-(3-chlorophenyl)-2-methylcyclopent-2-en-1-yl)(phenyl)methanone (2.28k)

According to the General Procedure **E**, 1-phenylnon-5-yn-1-one **2.21a** (18.6 mg, 0.1 mmol) reacted with 1-chloro-3-iodobenzene **2.27f** (28.6 mg, 0.12 mmol**)** following the general procedure. After purification by column chromatography (Hexane:Ethyl acetate = 40:1), **2.28k** was obtained as a colorless liquid (27.3 mg, 92%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.0 (d, J = 8.0 Hz, 2H), 7.6 (t, J = 6.9 Hz, 1H), 7.5 (t, J = 7.7 Hz, 2H), 7.3 (s, 1H), 7.3 – 7.2 (m, 1H), 7.2 (d, J = 9.2 Hz, 2H), 4.7 – 4.5 (m, 1H), 2.8 (dd, J = 4.2, 2.2 Hz, 2H), 2.4 – 2.3 (m, 1H), 2.2 – 2.0 (m, 1H), 1.8 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 201.8, 139.6, 137.8, 137.0, 134.5, 133.9, 133.1, 129.3, 128.7, 128.5, 127.9, 126.7, 126.0, 58.7, 36.2, 27.7, 14.8; **IR** (neat) 1672, 1577, 1211, 1177, 786, 750, 711, 694 cm^{-1}; HRMS (DART) m/z Calcd for $C_{19}H_{18}O_1Cl$ (MH^+): 297.1041; found: 297.1047.

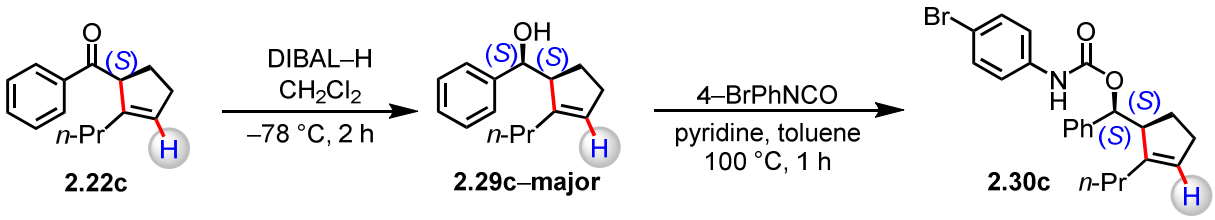


(2-methyl-3-(thiophen-2-yl)cyclopent-2-en-1-yl)(phenyl)methanone (2.28l)

According to the General Procedure **E**, 1-phenylnon-5-yn-1-one **2.21a** (18.6 mg, 0.1 mmol) reacted with 2-iodothiophene **2.27g** (25.2 mg, 0.12 mmol**)** following the general procedure. After purification by column chromatography (Hexane:Ethyl acetate = 40:1), **2.28l** was obtained as a white solid (22.8 mg, 85%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.1 – 8.0 (m, 2H), 7.6 (t, *J* = 7.4 Hz, 1H), 7.5 (t, *J* = 7.6 Hz, 2H), 7.3 – 7.2 (m, 1H), 7.0 (d, *J* = 4.5 Hz, 2H), 4.7 – 4.5 (m, 1H), 3.1 – 2.8 (m, 2H), 2.5 – 2.3 (m, 1H), 2.2 – 2.0 (m, 1H), 2.0 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 201.8, 140.0, 136.9, 133.0, 132.8, 132.1, 128.6, 128.5, 126.7, 125.0, 124.4, 59.4, 36.2, 27.6, 15.6; **IR** (neat) 1674, 1594, 1374, 1338, 1177, 1158, 694 cm^{-1}; HRMS (DART) m/z Calcd for $C_{17}H_{17}O_1S$ (MH^+):269.0995; found: 269.0994.

2.6.4 Determination of Absolute Configuration

To determine the absolute configuration of **2.22c**, it was first transformed to **2.30c** according to a literature procedure.[22] **2.30c** was then recrystallized and its X-ray crystallographic analysis was carried out as described below.



(*S*)-Phenyl((*S*)-2-propylcyclopent-2-en-1-yl)methanol (2.29c–major)

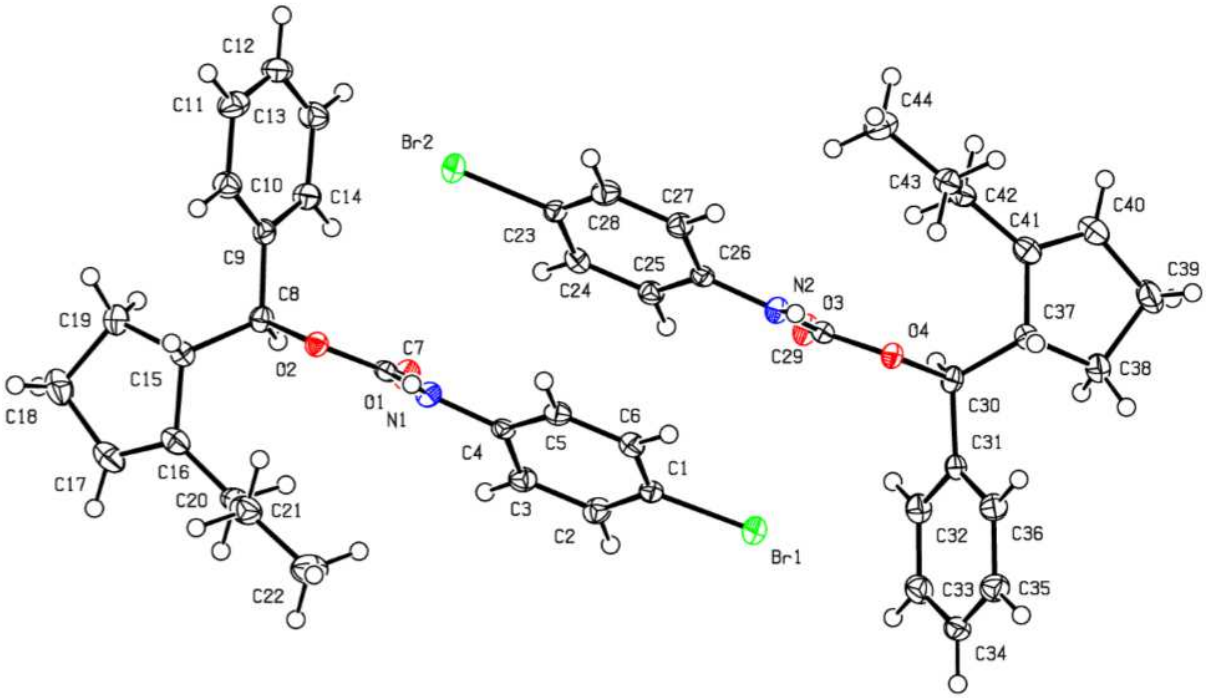
To a solution of (*S*)-phenyl(2-propylcyclopent-2-en-1-yl)methanone **2.22c** (642 mg, 3.0 mmol 1.0 equiv.) in CH_2Cl_2 (0.1 M) was added DIBAL-H (1.7 g, 12 mmol, 4.0 equiv.), dropwise at −78 °C. The reaction mixture was allowed to stir for 2 h at −78 °C. Then, 1N HCl (30 mL) was added to the solution. The reaction mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (2 x 50 mL) and dried over Na_2SO_4. After filtration and removal of the solvent, ^{1}H NMR analysis of the crude material revealed that **2.29c-major** and **2.29c-minor** were obtained in the ratio of 1.2:1.0. The crude material was purified by silica gel column chromatography (1.0 % Et_2O in hexanes) to give compound **2.29c-major** (314 mg, 48%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 4H), 7.26 – 7.21 (m, 1H), 5.45 (s, 1H), 4.73 (t, J = 5.1 Hz, 1H), 3.07 – 3.01 (m, 1H), 2.19 – 1.95 (m, 3H), 1.94 – 1.79 (m, 3H), 1.72 (ddd, J = 12.7, 8.6, 4.3 Hz, 1H), 1.52 – 1.33 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H).

[22] (a) Wadamoto, M.; Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 10098–10099. (b) Petrone, D. A.; Isomura, M.; Franzoni, I.; Rössler, S. L.; Carreira, E.M. *J. Am. Chem. Soc.* **2018**, *140*, 4697–4704.

(*S*)-Phenyl((*S*)-2-propylcyclopent-2-en-1-yl)methyl (4-bromophenyl)carbamate (2.30c)

To a solution of **2.29c-major** (151 mg, 0.70 mmol, 1.0 equiv.) in toluene (0.035 M) were added *p*-bromophenyl isocyanate (416 mg, 2.1 mmol, 3.0 equiv.) and pyridine (277 mg, 3.5 mmol, 5.0 equiv.). The resulting heterogeneous solution was allowed to stir at 100 °C for 1 h. The solution was then cooled and filtered through a short plug of Celite using CH_2Cl_2. The filtrate was concentrated and the residue was purified by silica gel column chromatography (10 % EtOAc in hexanes) to give compound **2.30c** (261 mg, 90%) as a white solid. **2.30c** was recrystallized using the vapor-vapor diffusion method, using EtOH to dissolve the product in an inner vial, and pentane as the precipitant placed in the outer vial in order for slow diffusion to occur into the inner vial. The solution was placed at 0 °C, whereupon a crystal was obtained for X-ray crystallographic analysis which revealed that the absolute configuration of **2.30c** is (*S,S*); see **2.6.7** for X-ray crystallographic data.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 5.5 Hz, 4H), 7.30 – 7.24 (m, 4H), 6.64 (s, 1H), 5.74 (d, J = 6.6 Hz, 1H), 5.43 (s, 1H), 3.19 – 3.10 (m, 1H), 2.23 – 2.07 (m, 2H), 2.07 – 1.96 (m, 1H), 1.84 – 1.73 (m, 2H), 1.73 – 1.63 (m, 1H), 1.63 – 1.53 (m, 1H), 1.53 – 1.43 (m, 1H), 0.91 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.55, 144.32, 138.95, 136.99, 131.93, 127.99, 127.71, 127.48, 126.82, 120.21, 115.91, 79.11, 51.32, 32.57, 30.45, 26.88, 21.06, 14.10; **IR** (neat) 3313, 2953, 2926, 1697, 1592, 1530, 1488, 1396, 1305, 1217, 1073, 1045, 822, 698 cm^{-1}; **HRMS** (DART) Calcd for $C_{22}H_{25}NO_2Br$ (MH^+): 414.10632; found: 414.10436; **HPLC** (Chiralcel OD-H; 5%/ 95% isopropanol/ hexanes, 1.0 mL/min; tr = 13.8 min (major), 7.0 min (minor); 97:3 er); $[\alpha]^{25}_D$ = –46.0° (c = 1.0, CH_2Cl_2).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C8
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O4
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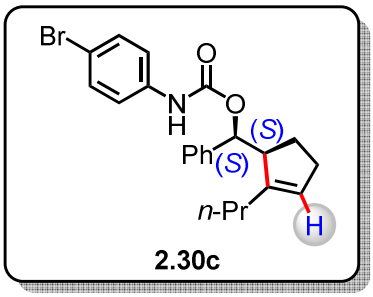
C34



2.30c

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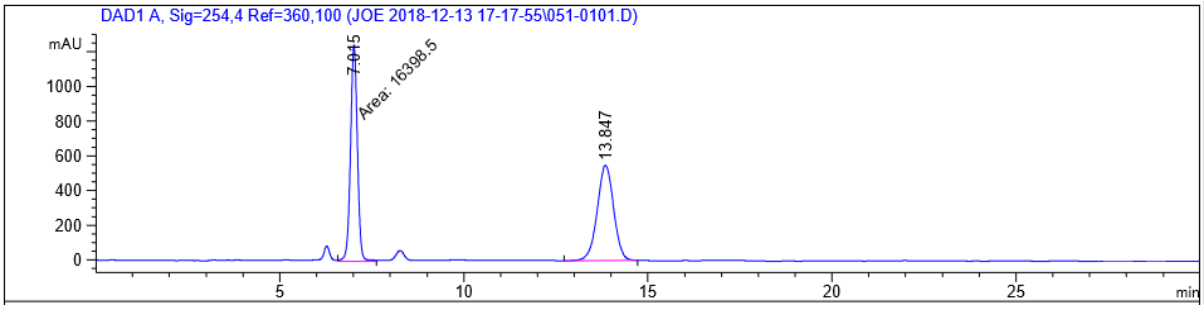

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Totals :				3.33821e4	1797.83636	

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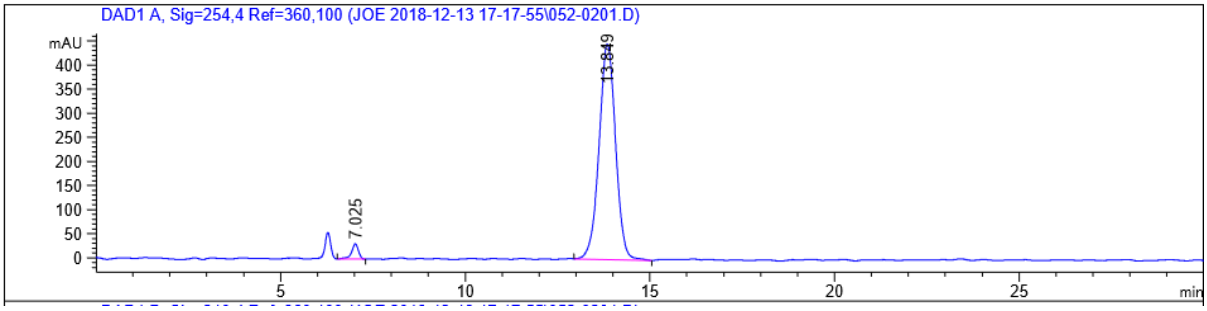

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

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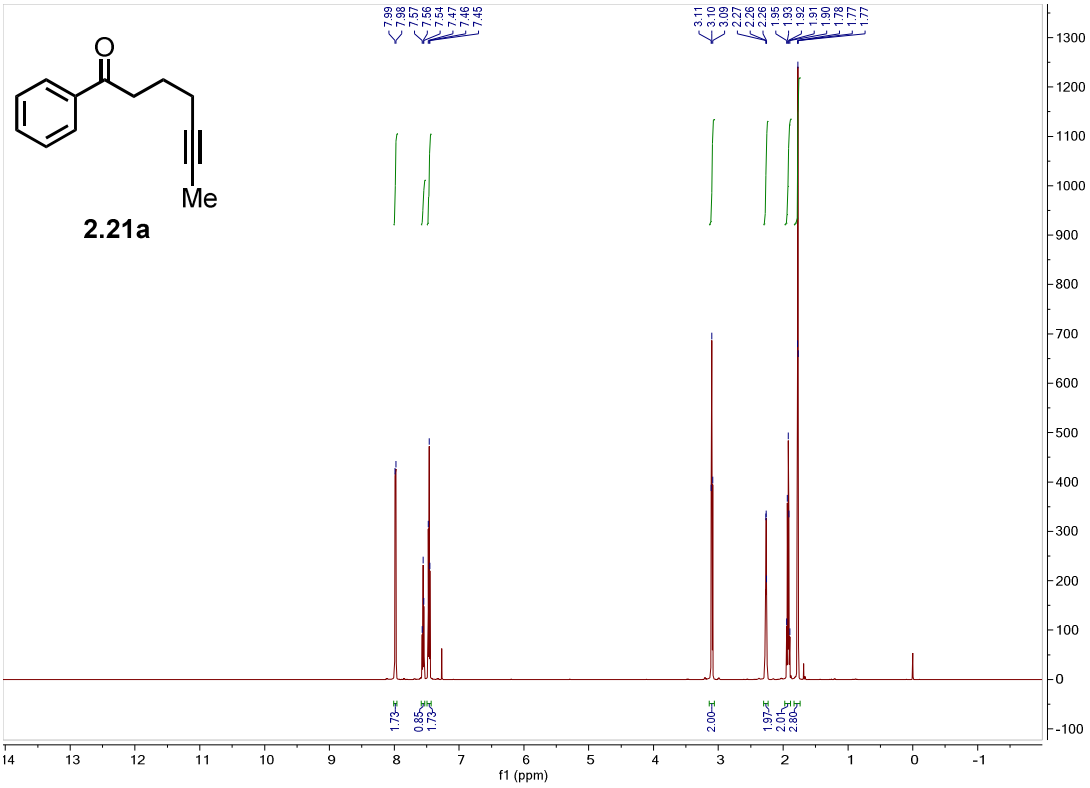
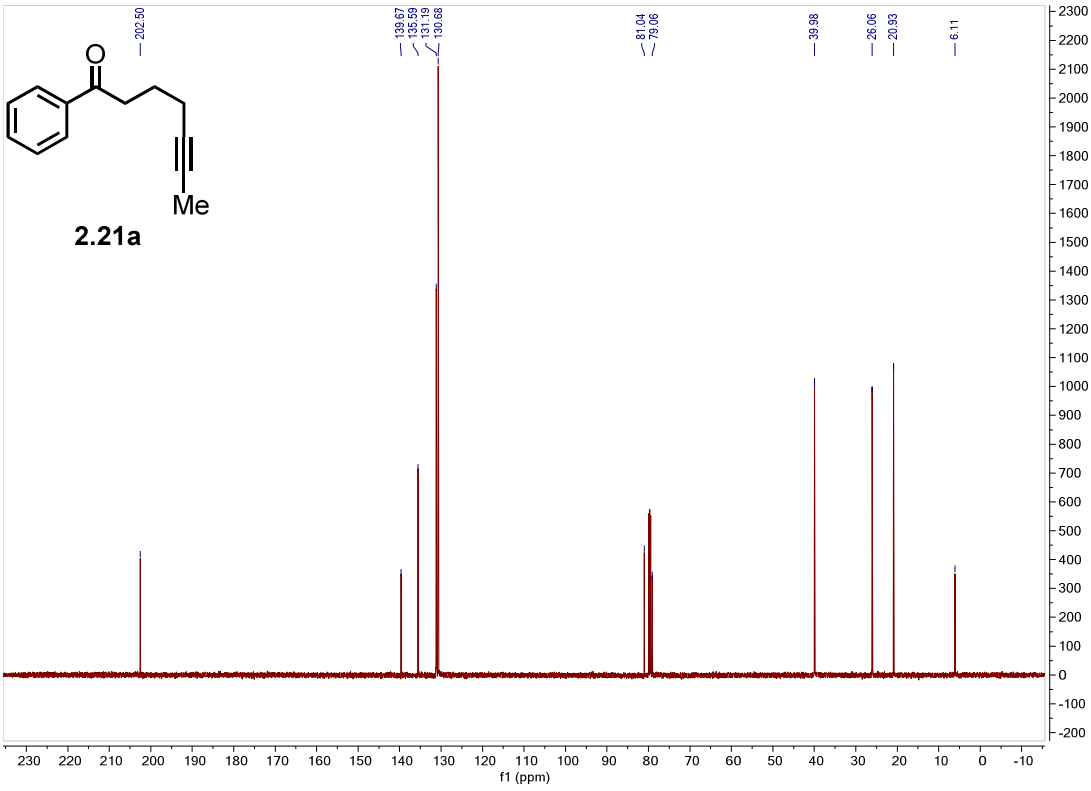
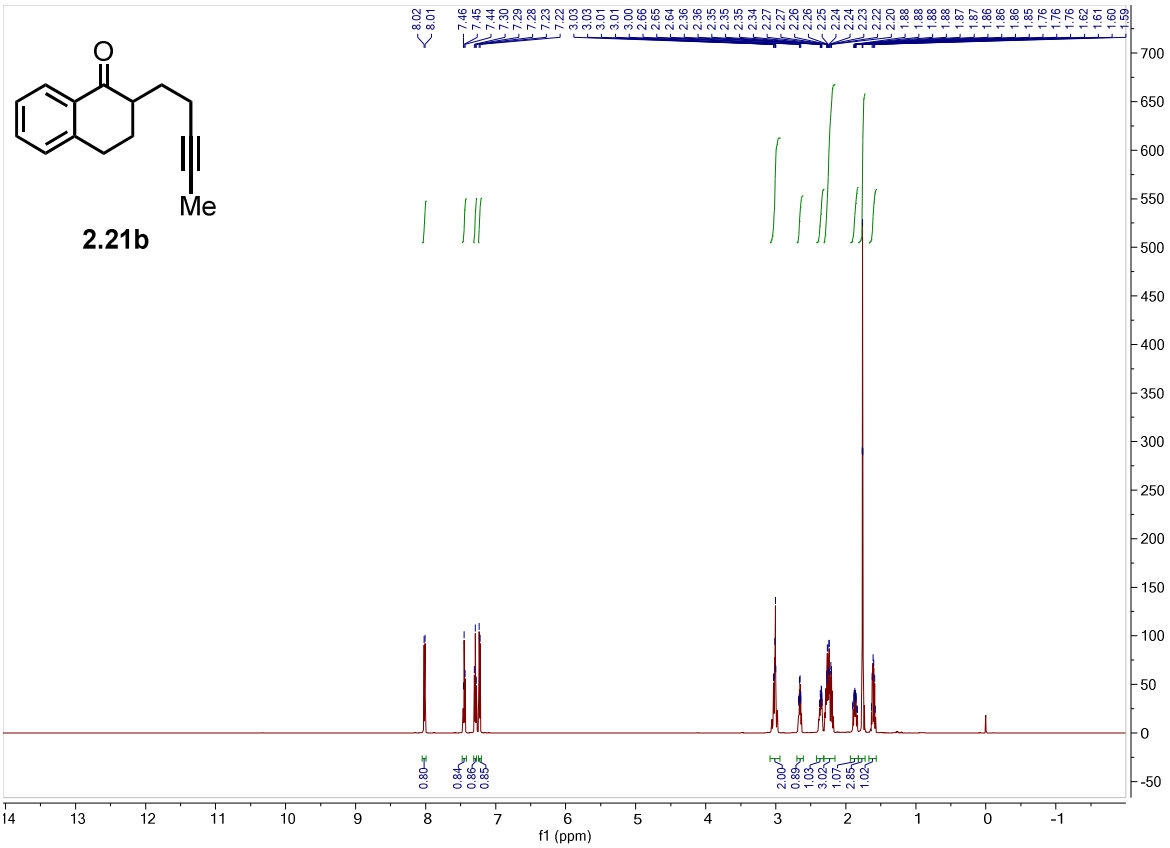
2.6.5 NMR Spectra for New Compounds



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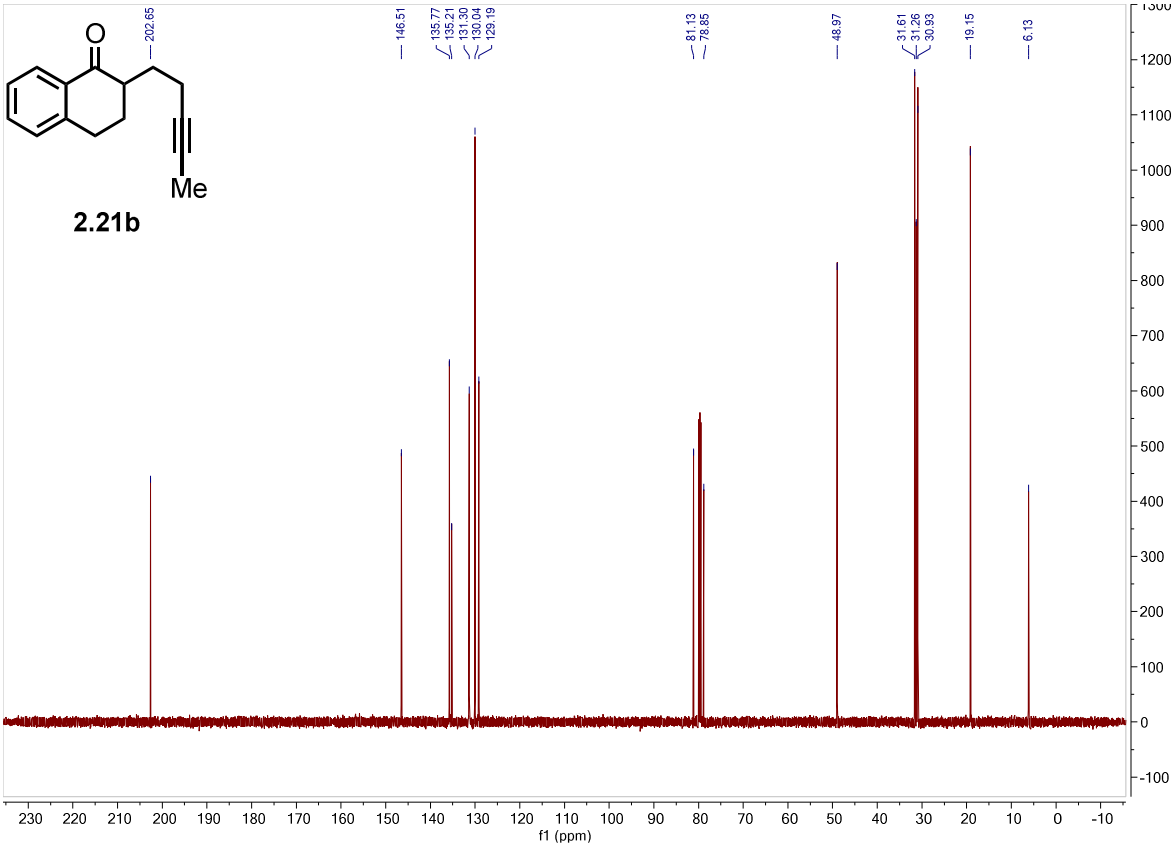
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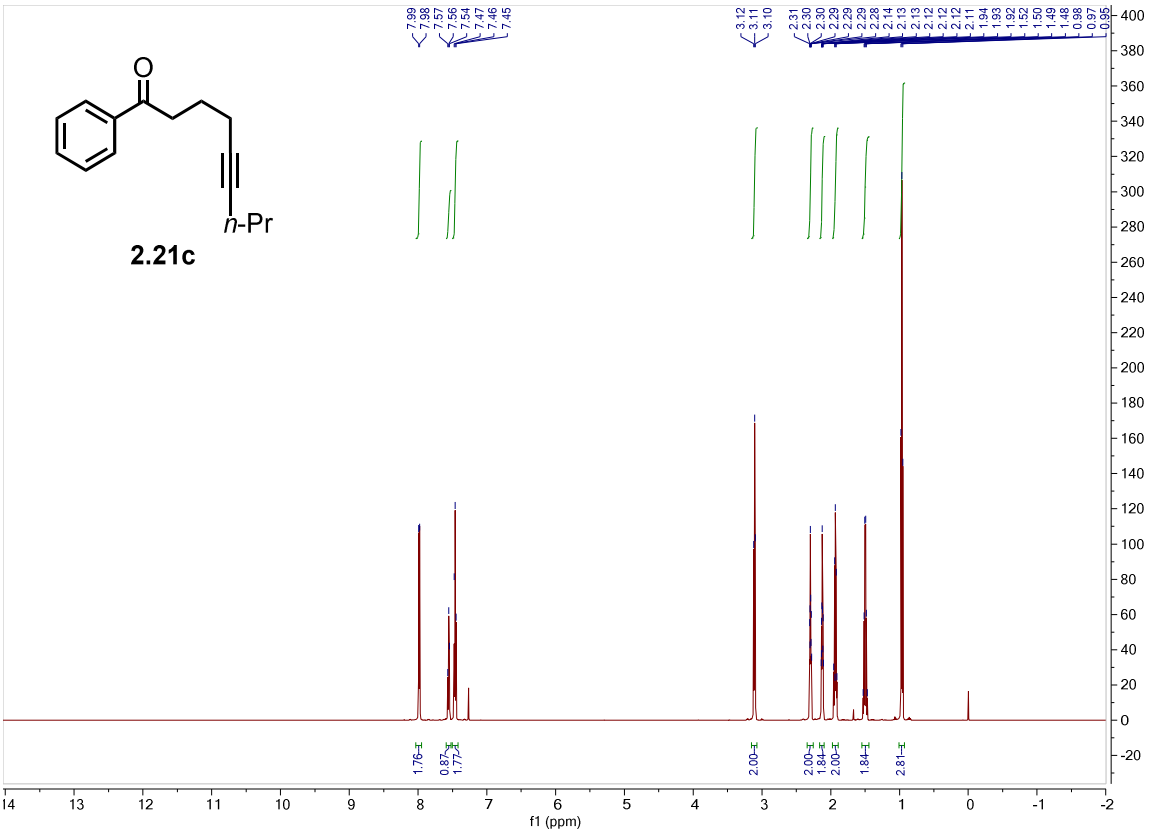
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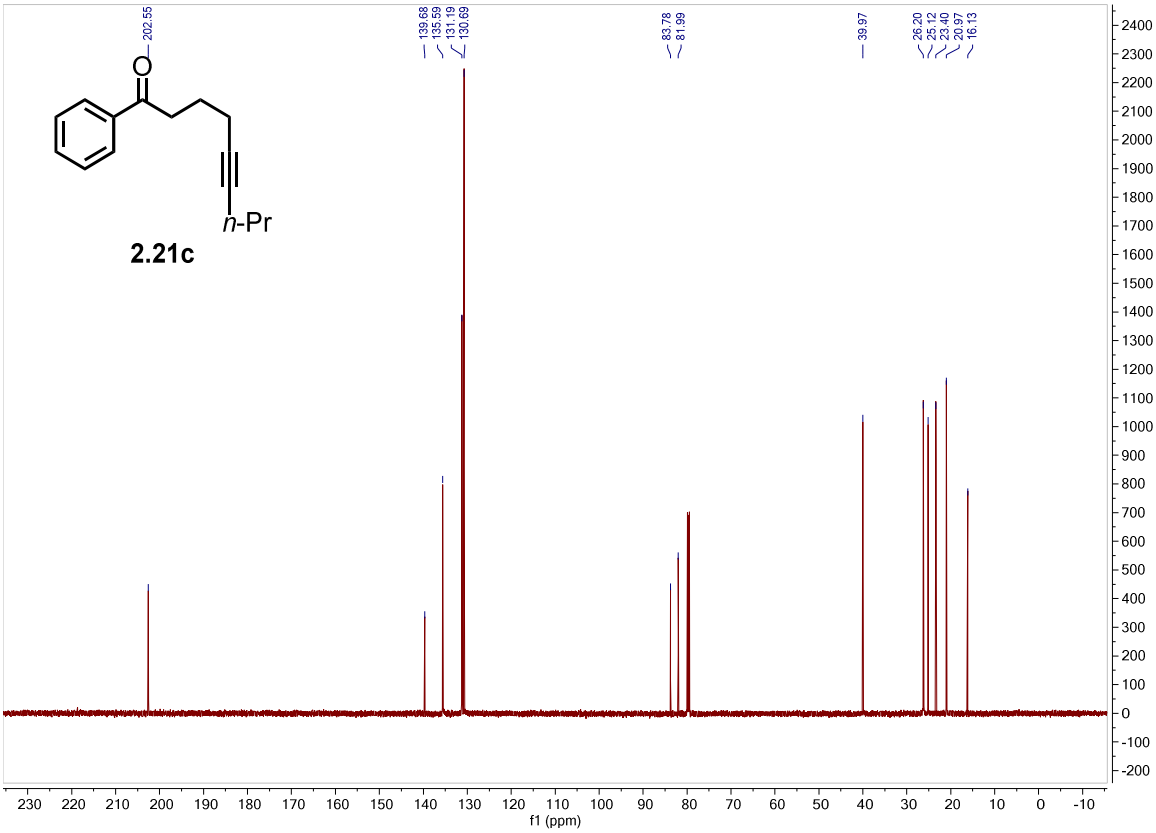
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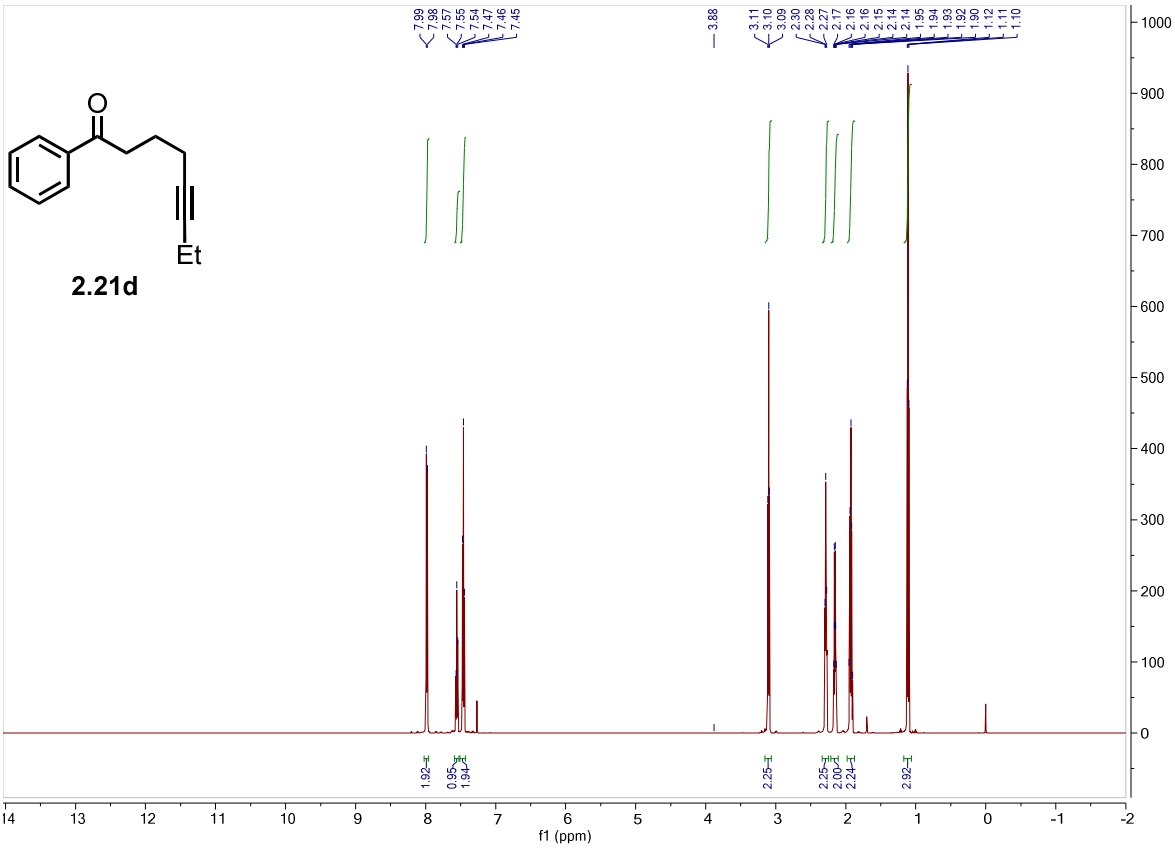
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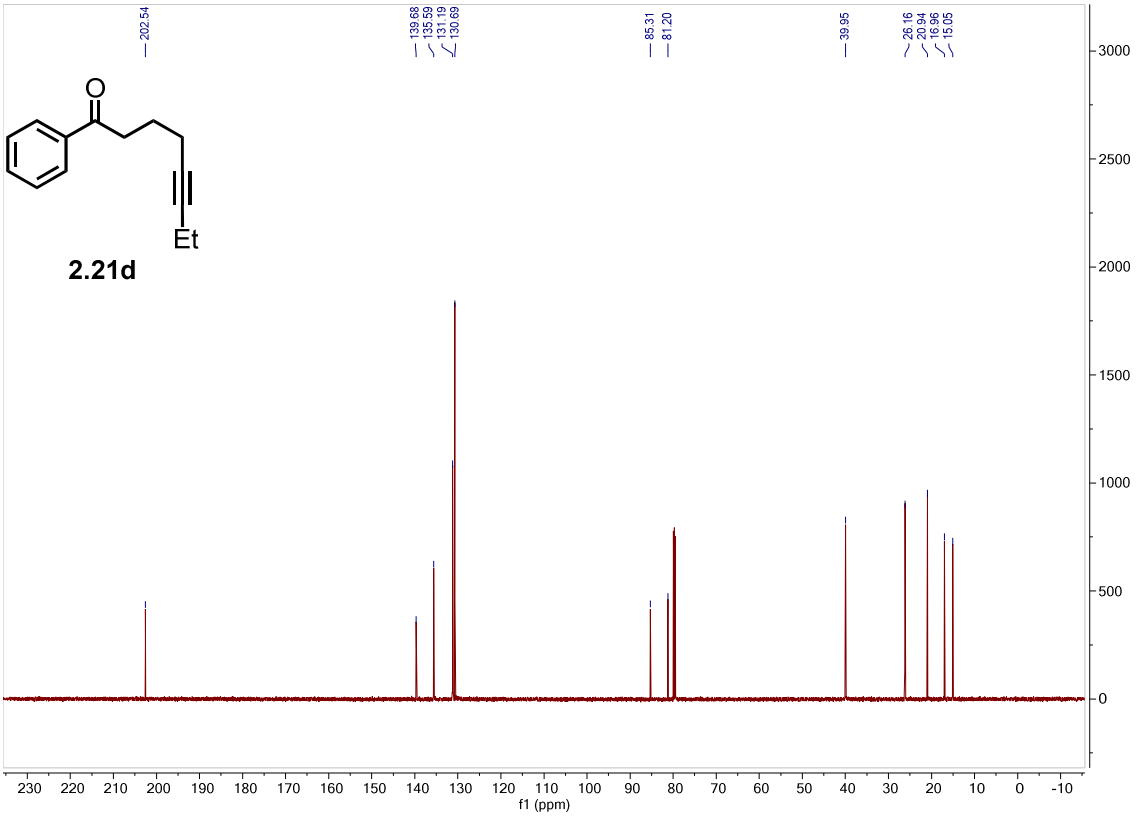
2.92
f1 (ppm)
O
Et
2.21d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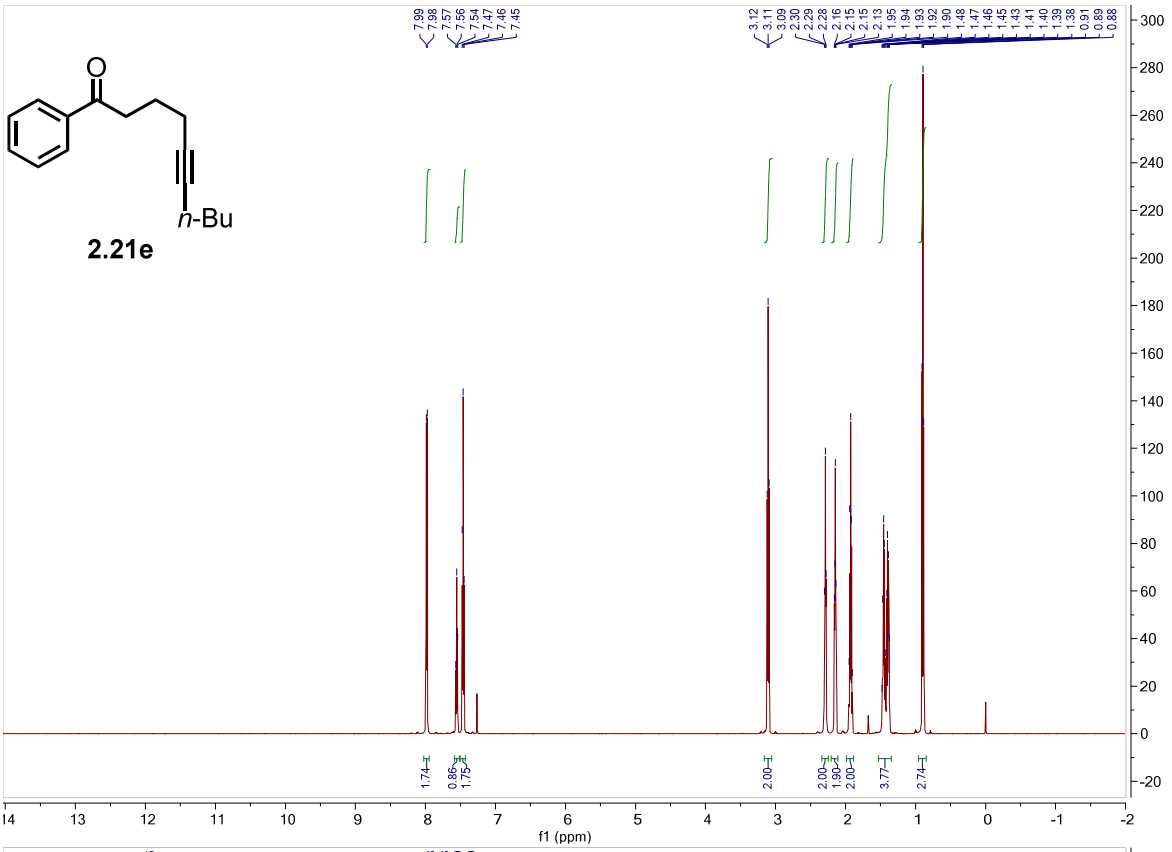
O
Et
2.21d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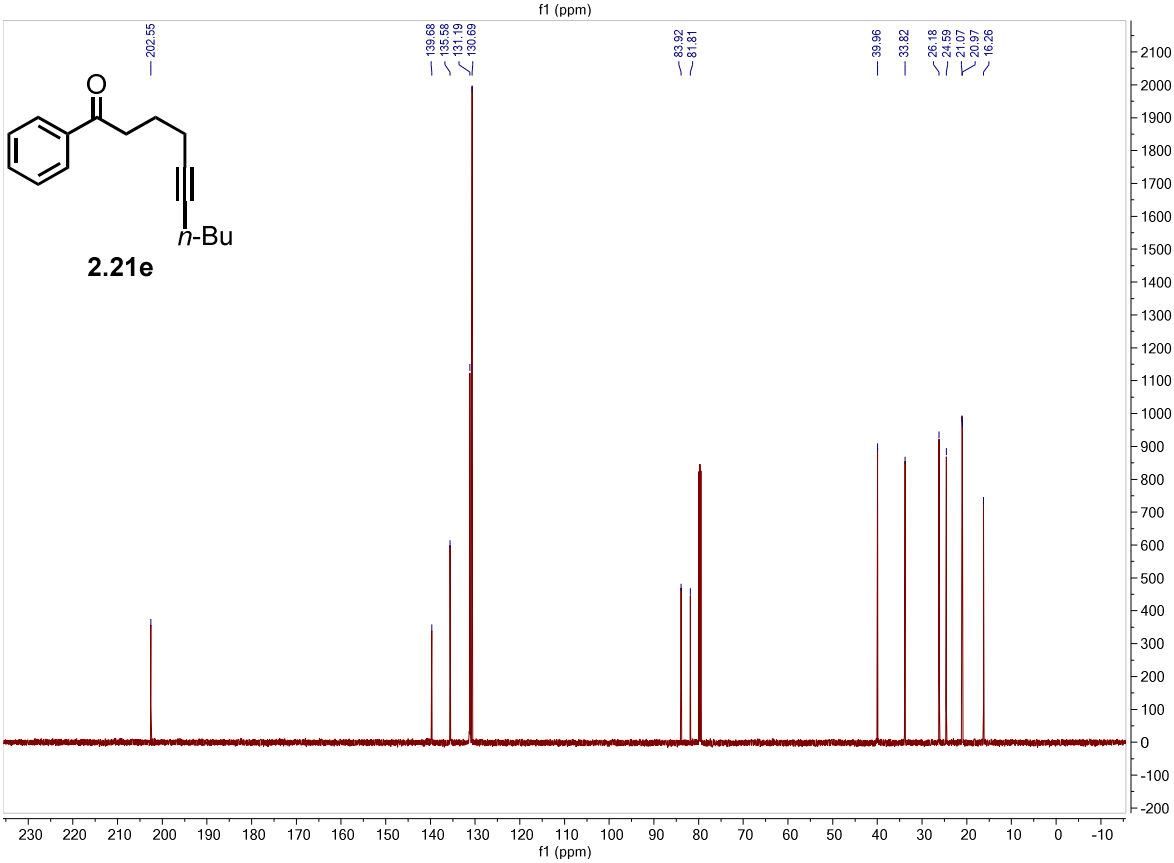
f1 (ppm)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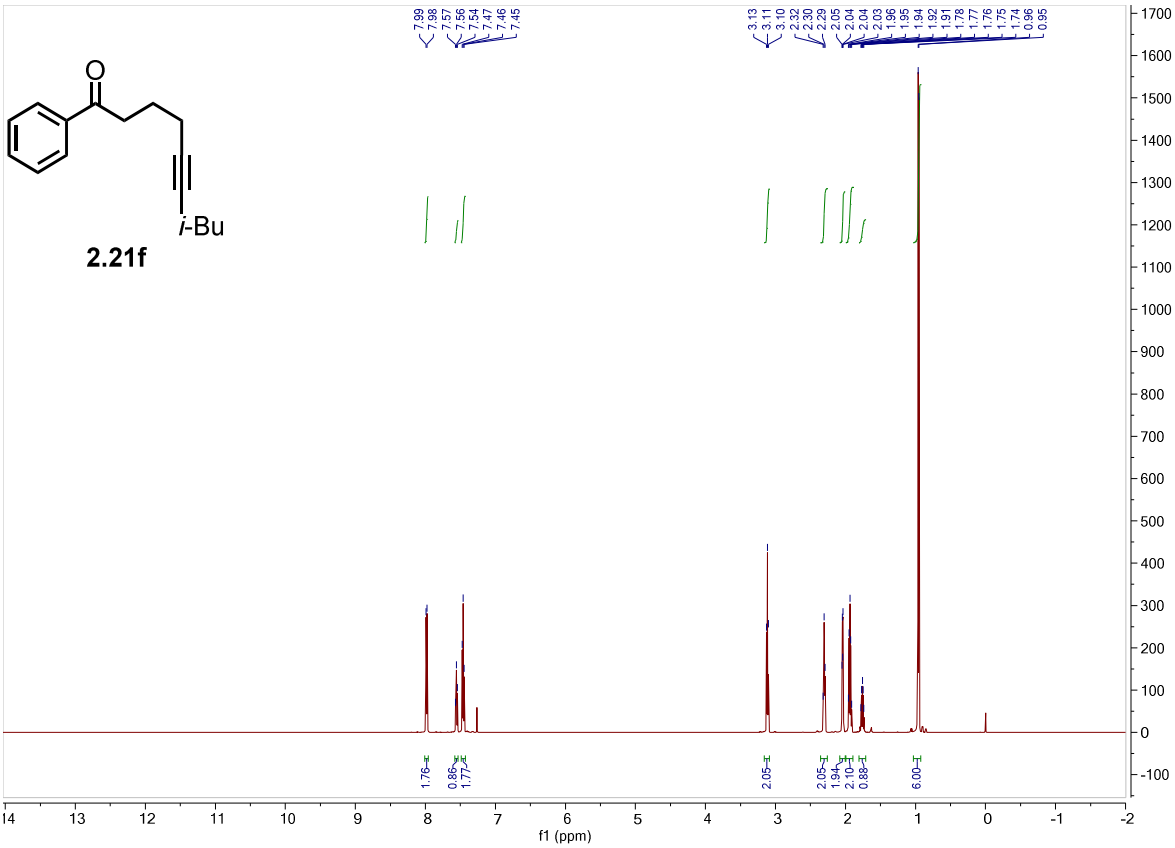
2.21e
f1 (ppm)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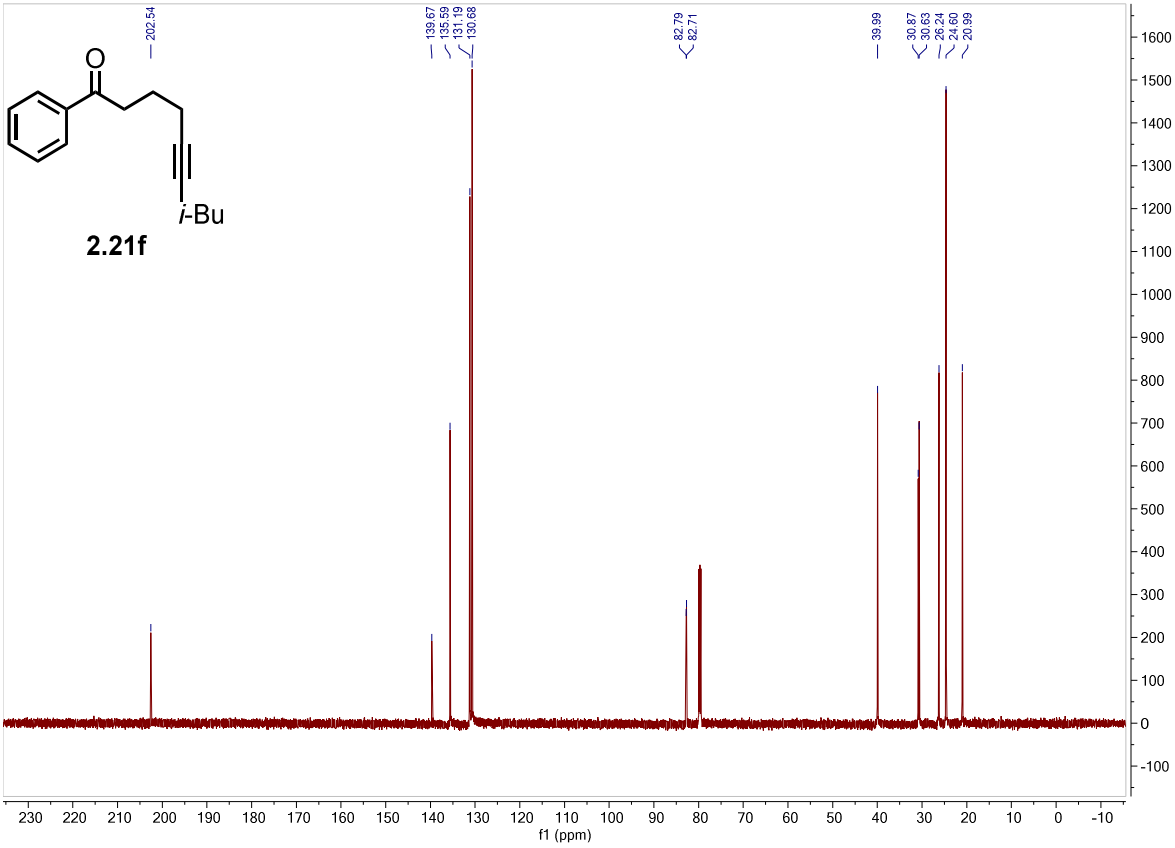
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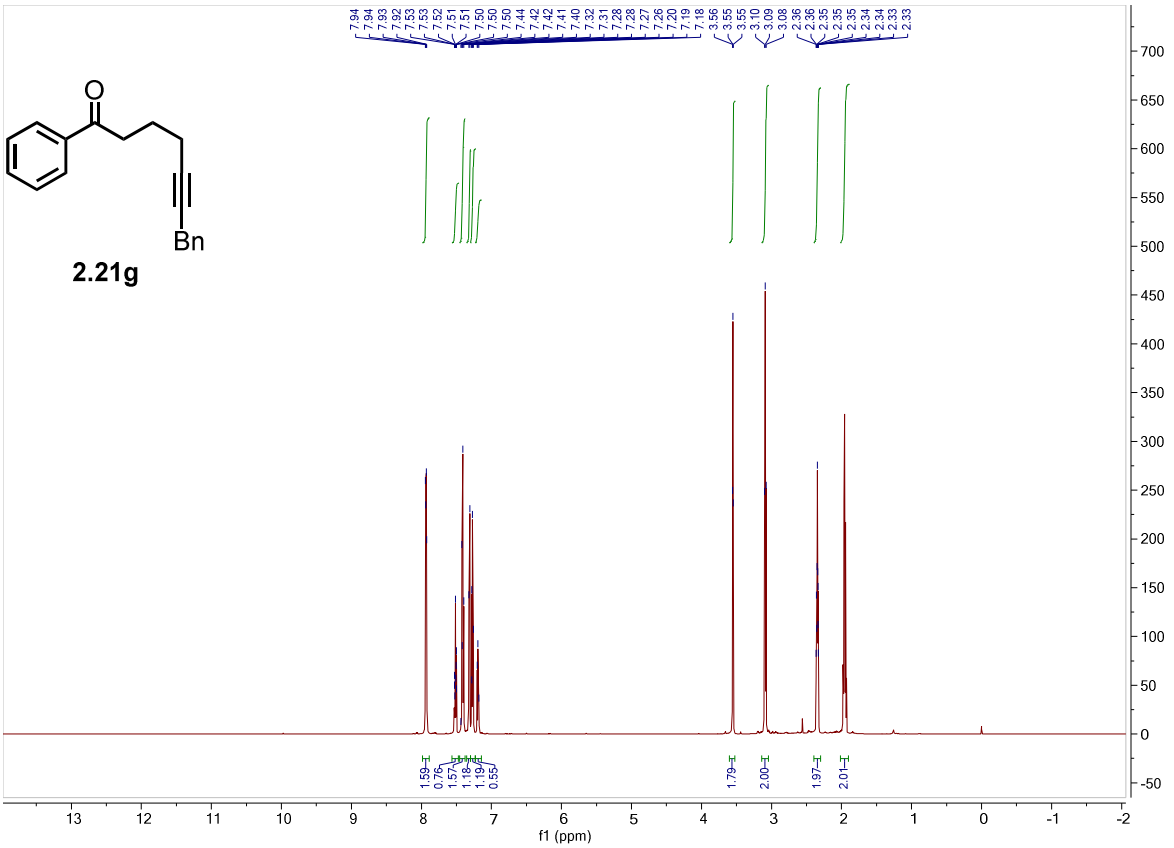
f1 (ppm)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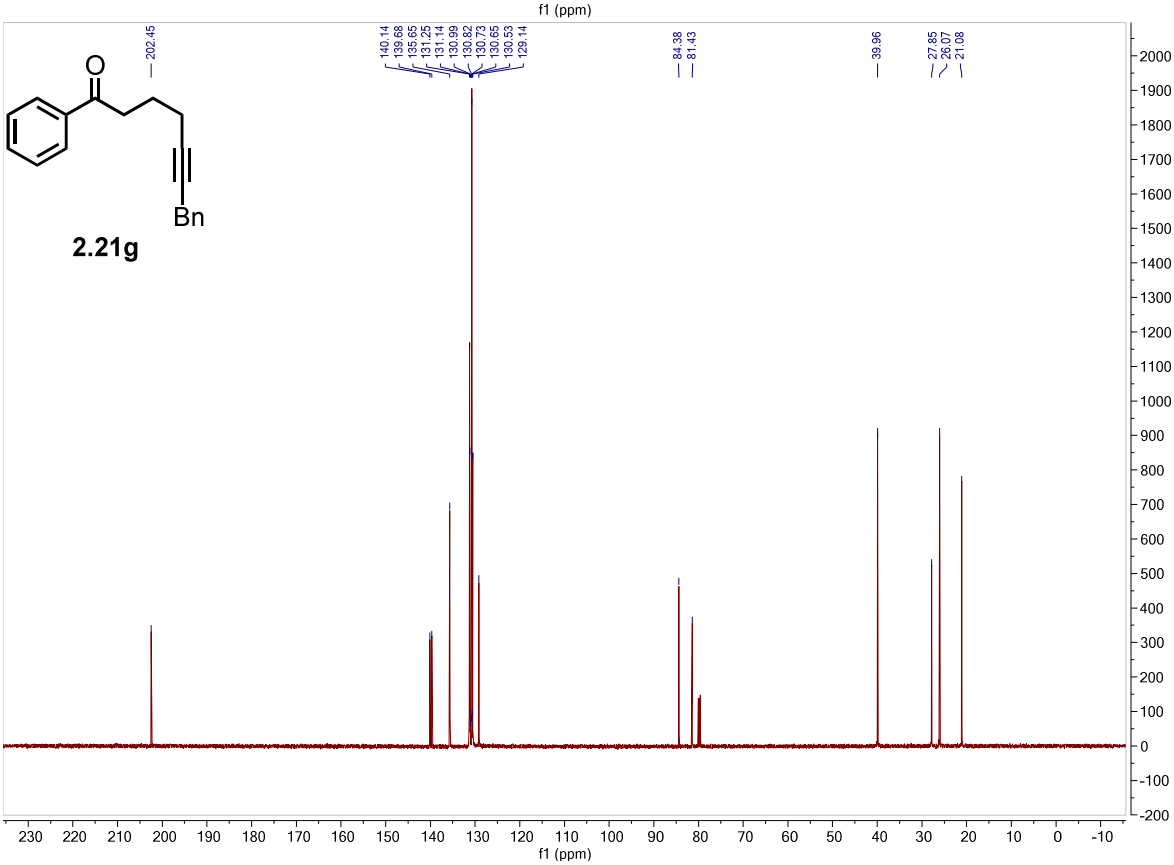
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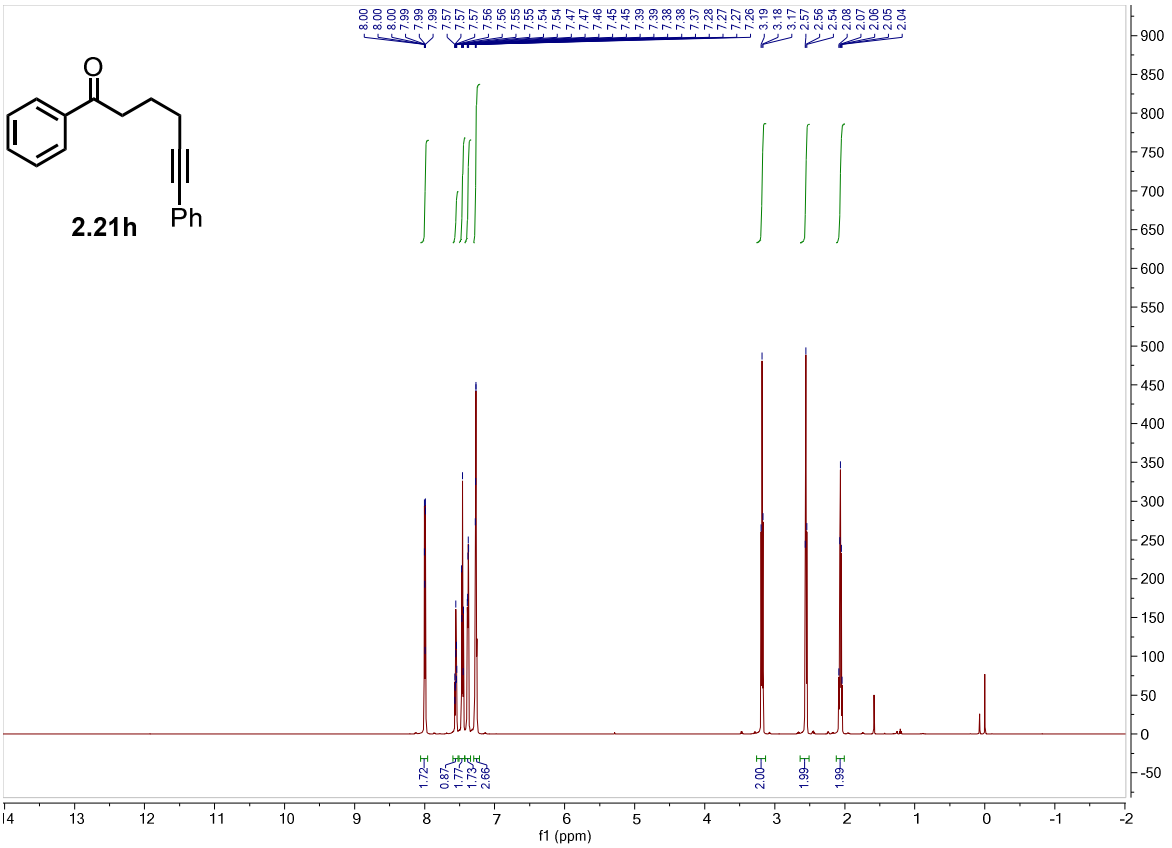
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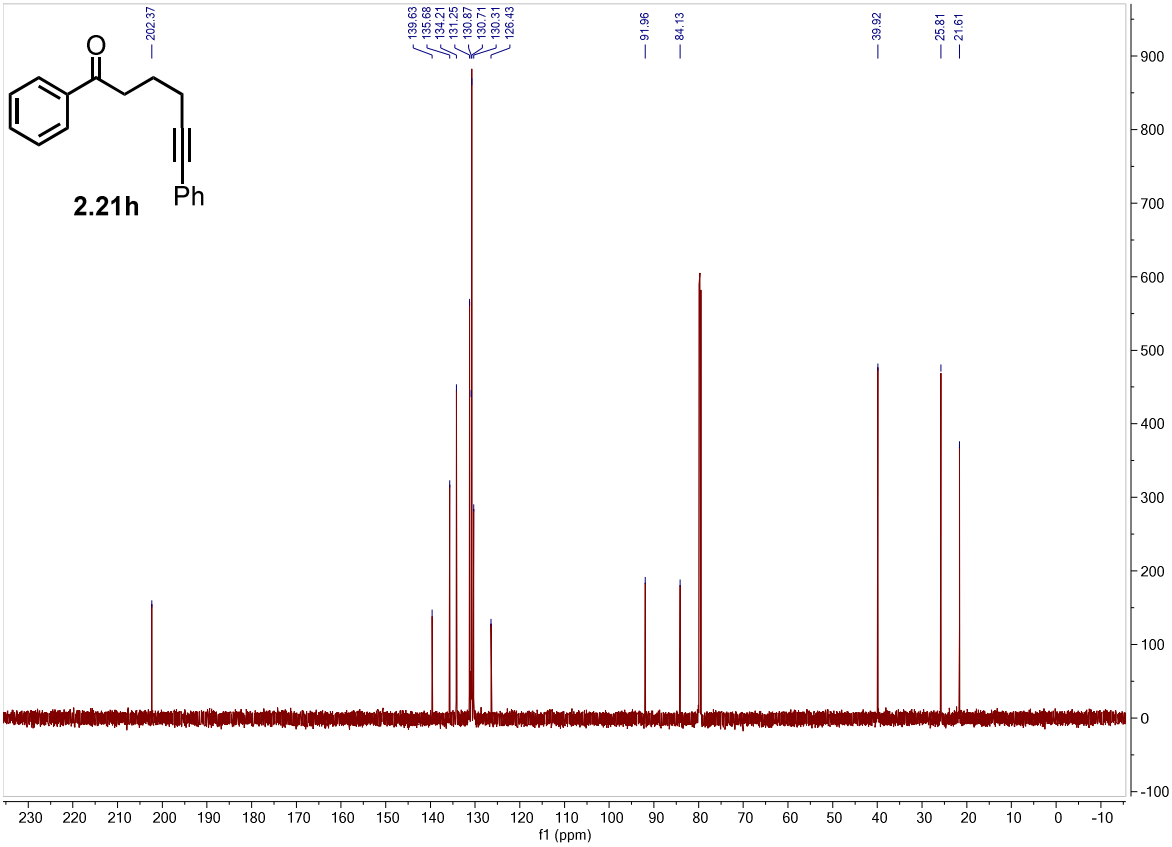
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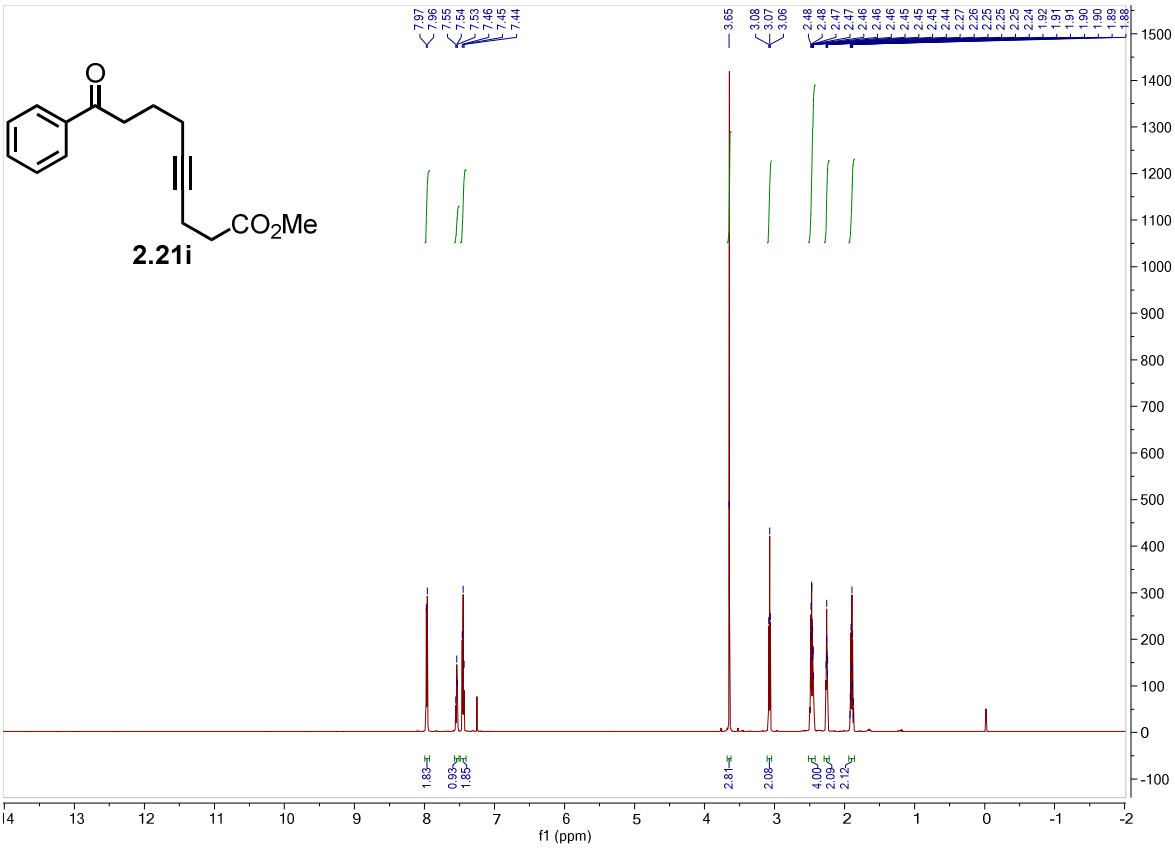
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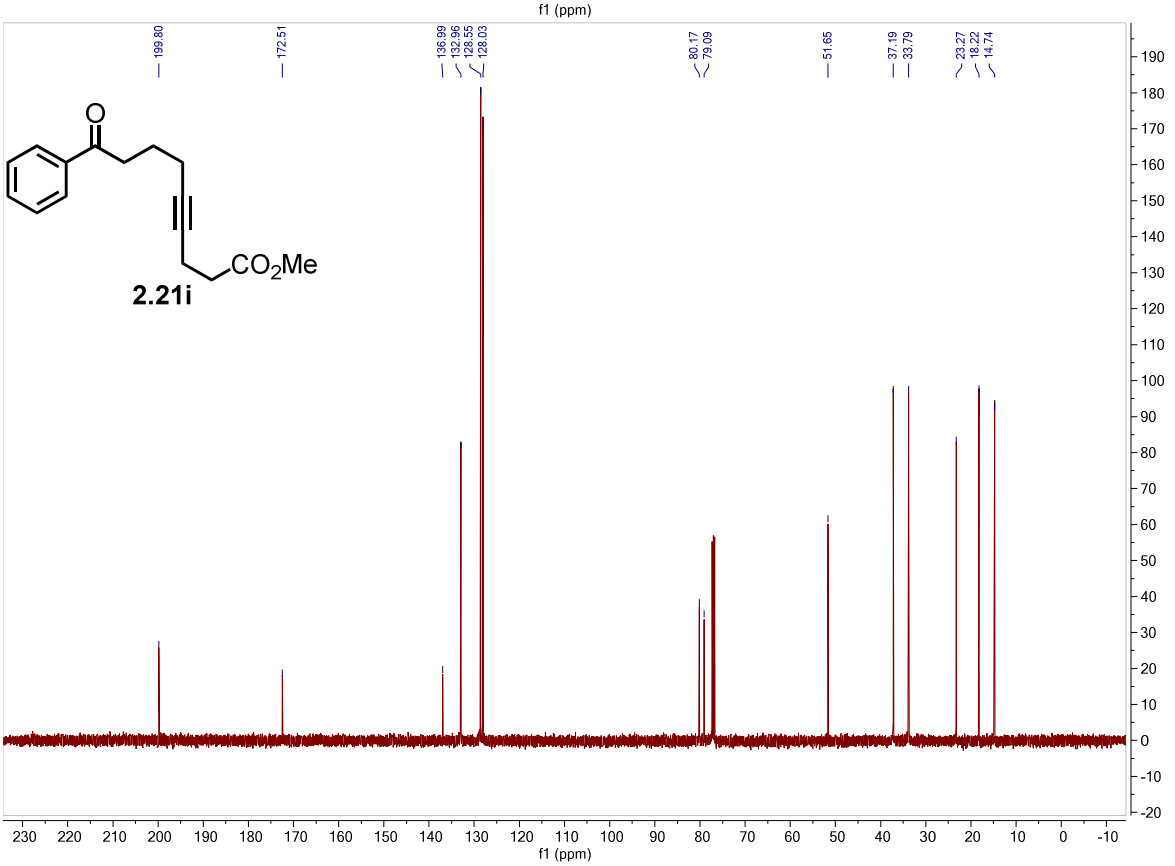
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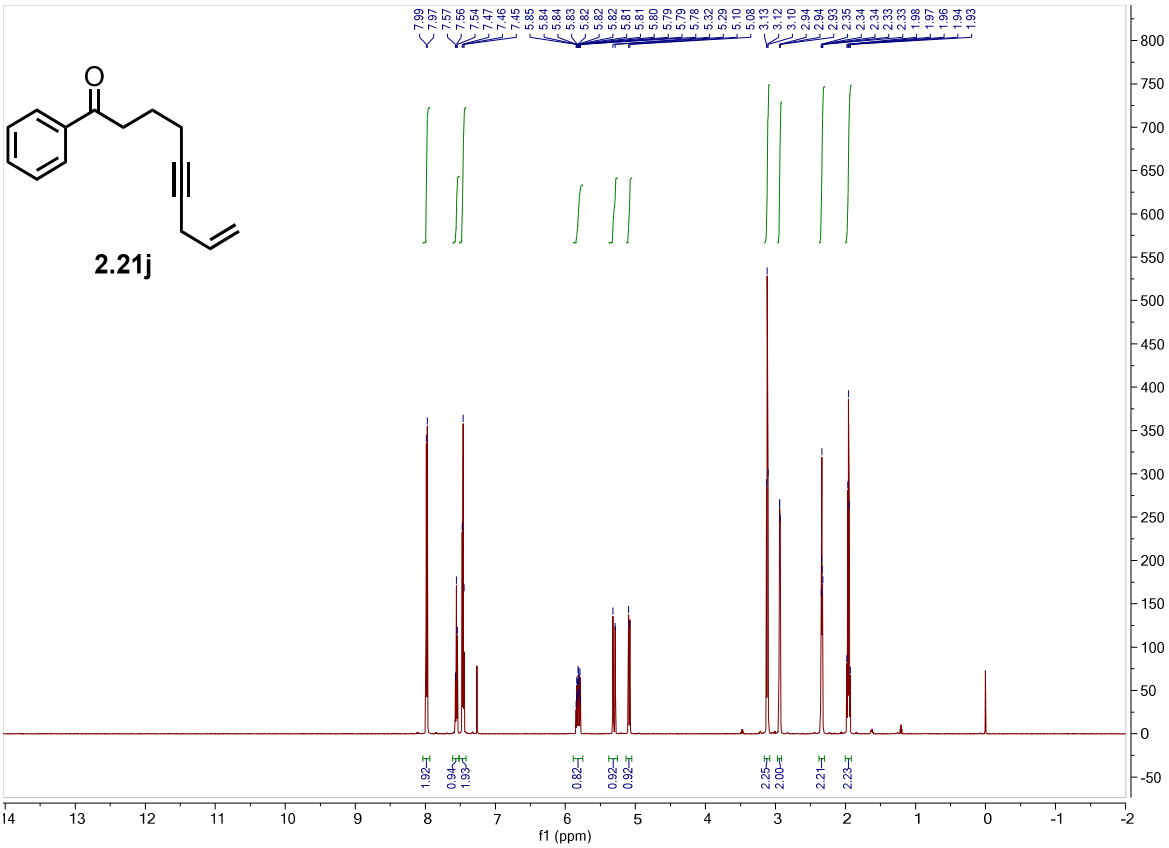
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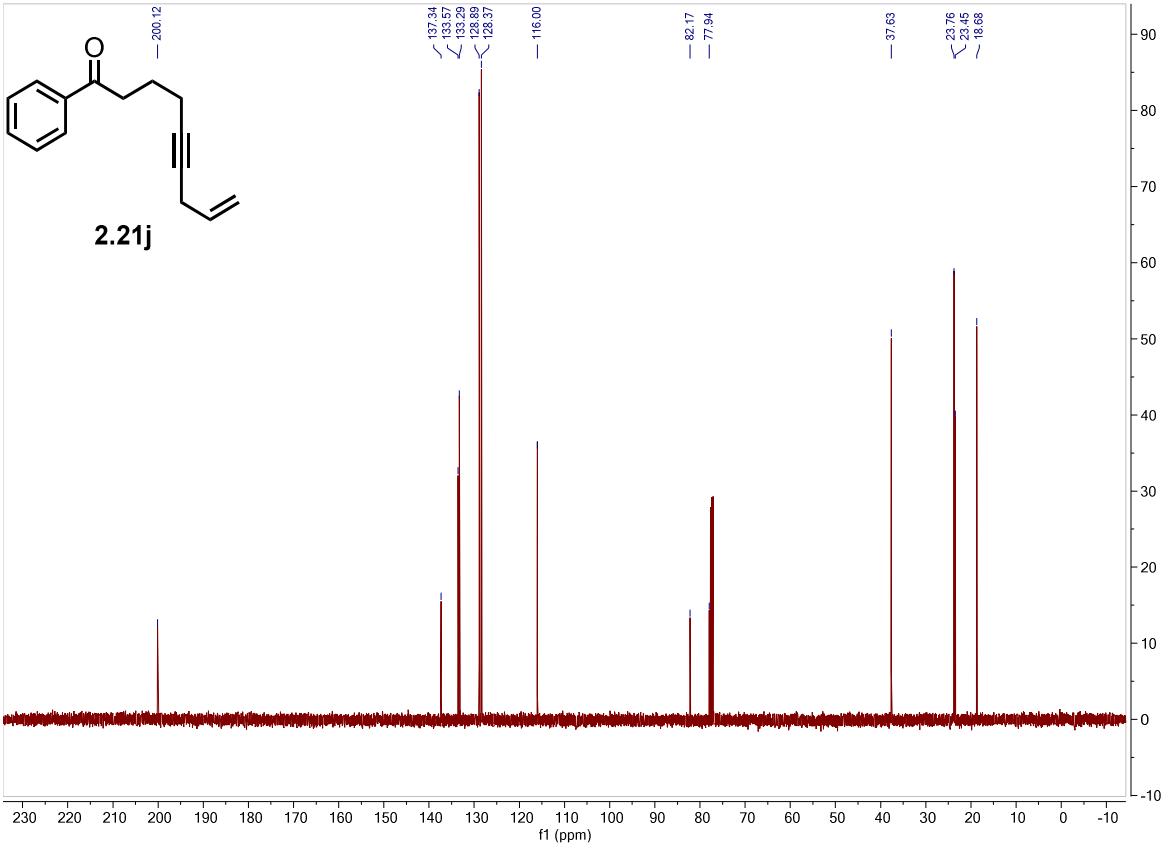
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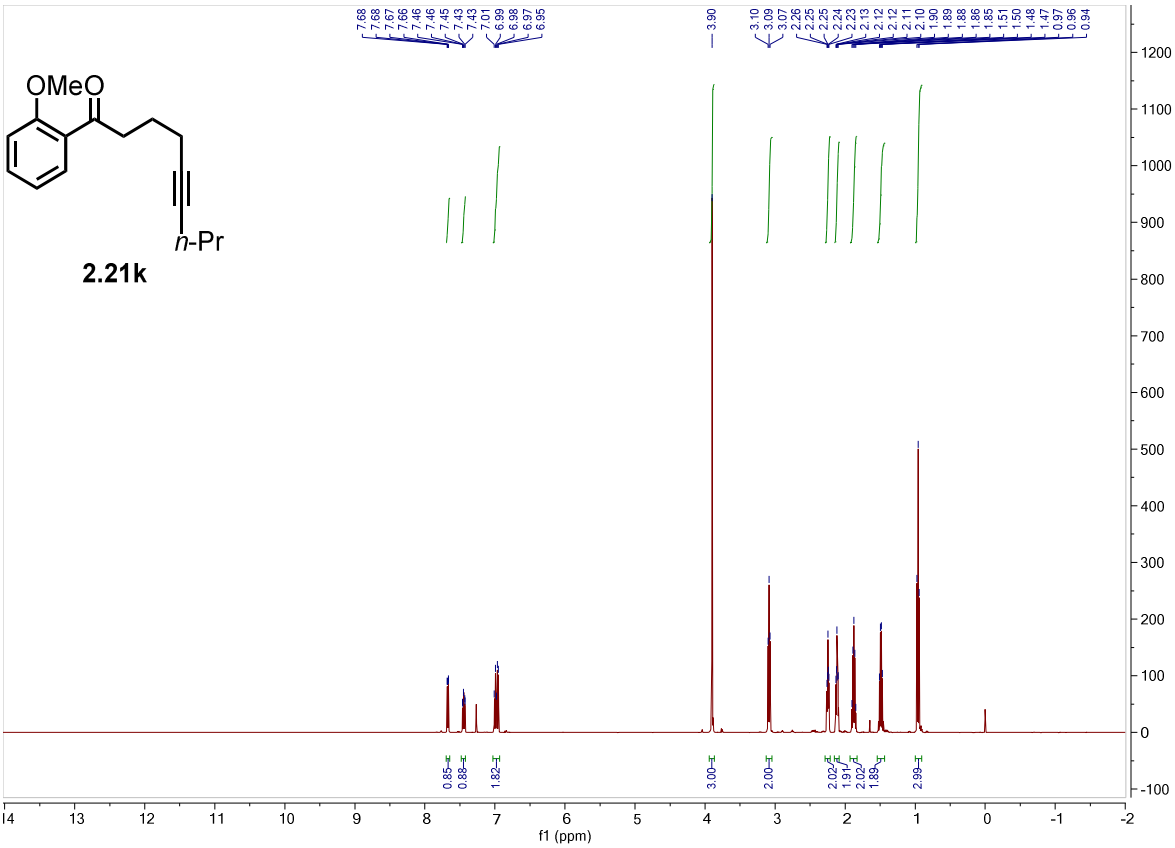
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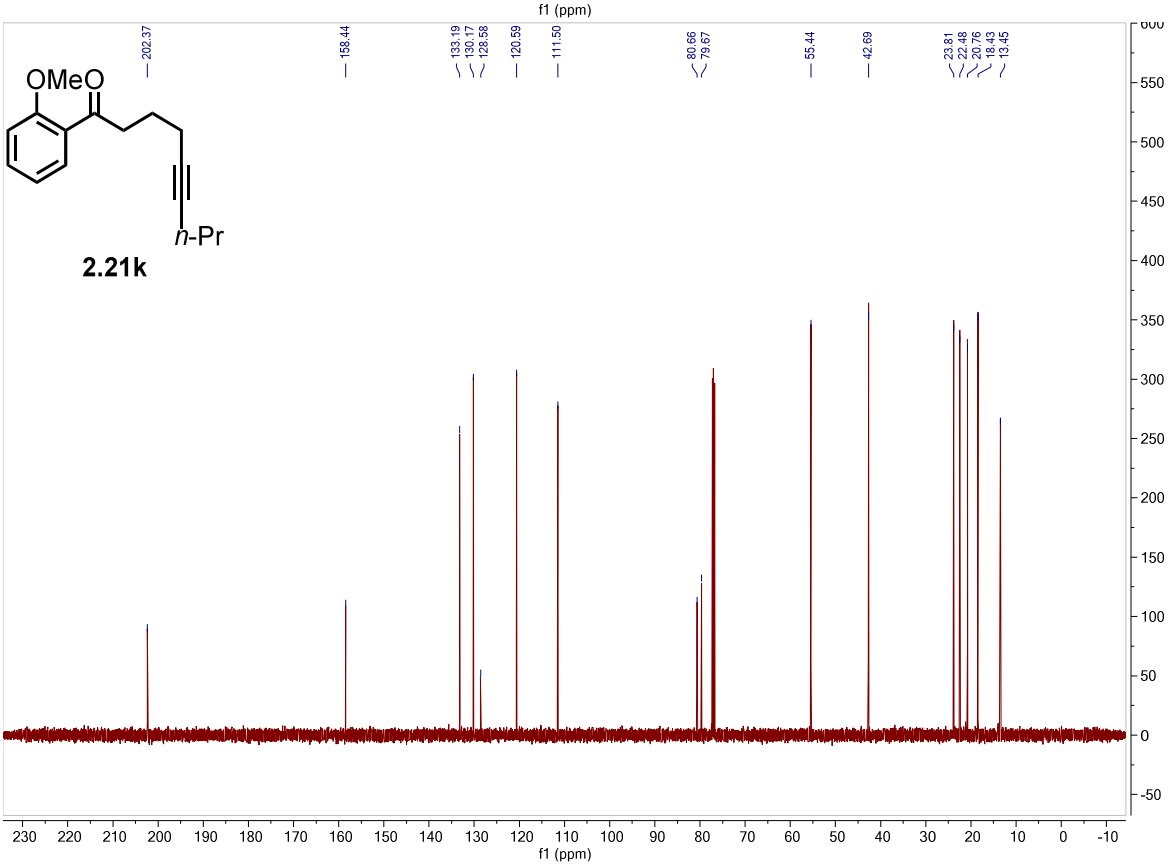
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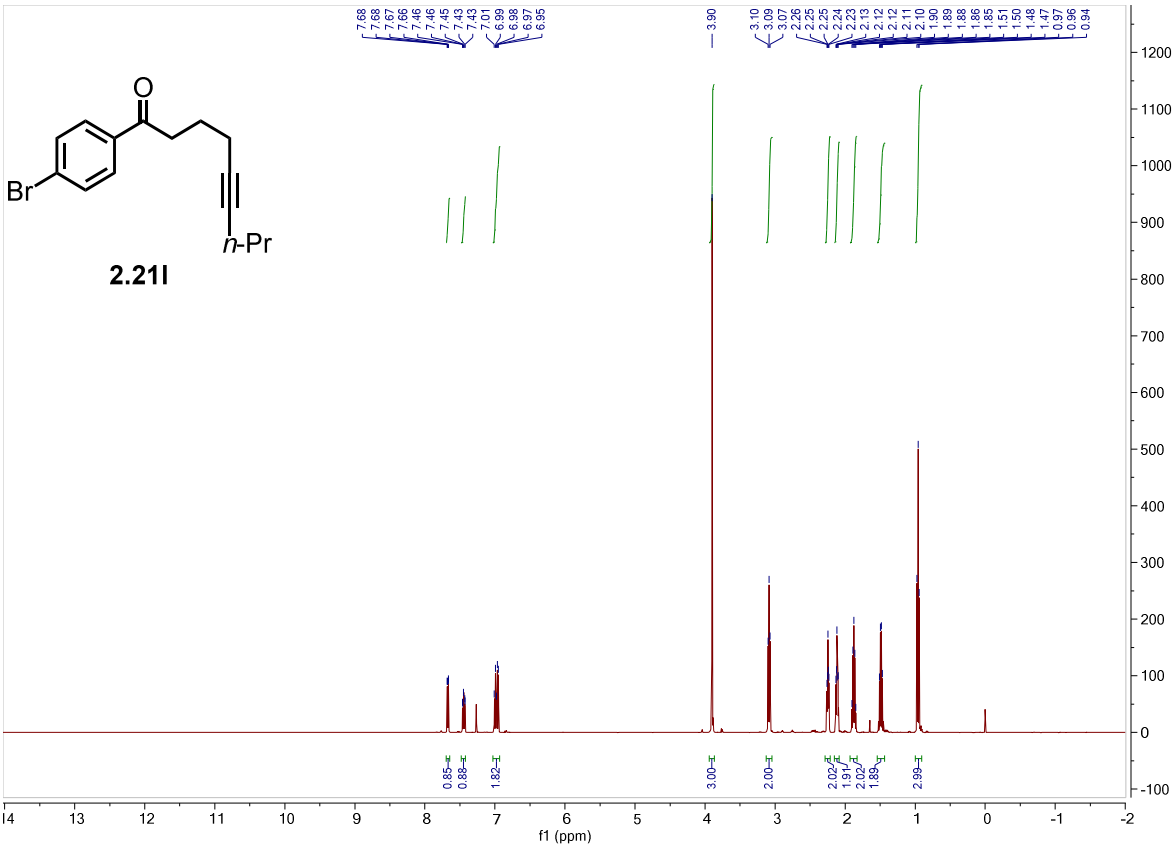
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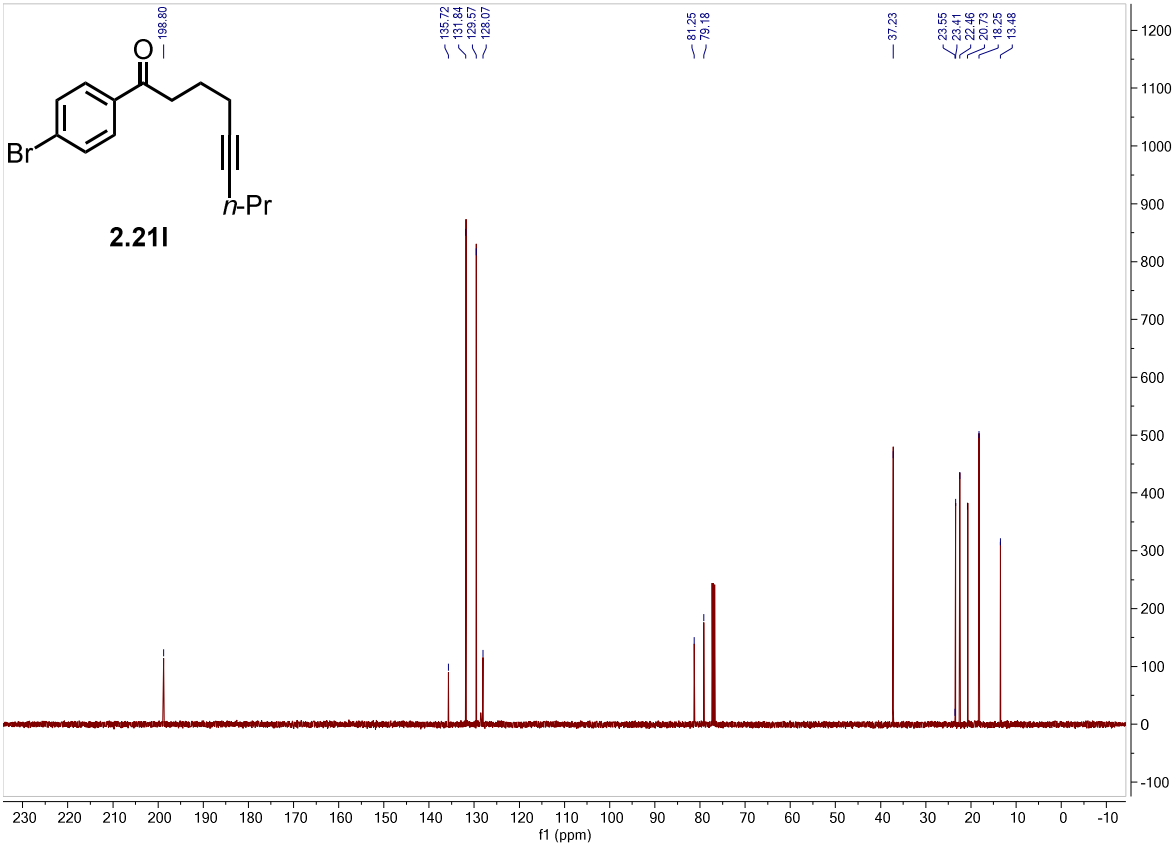
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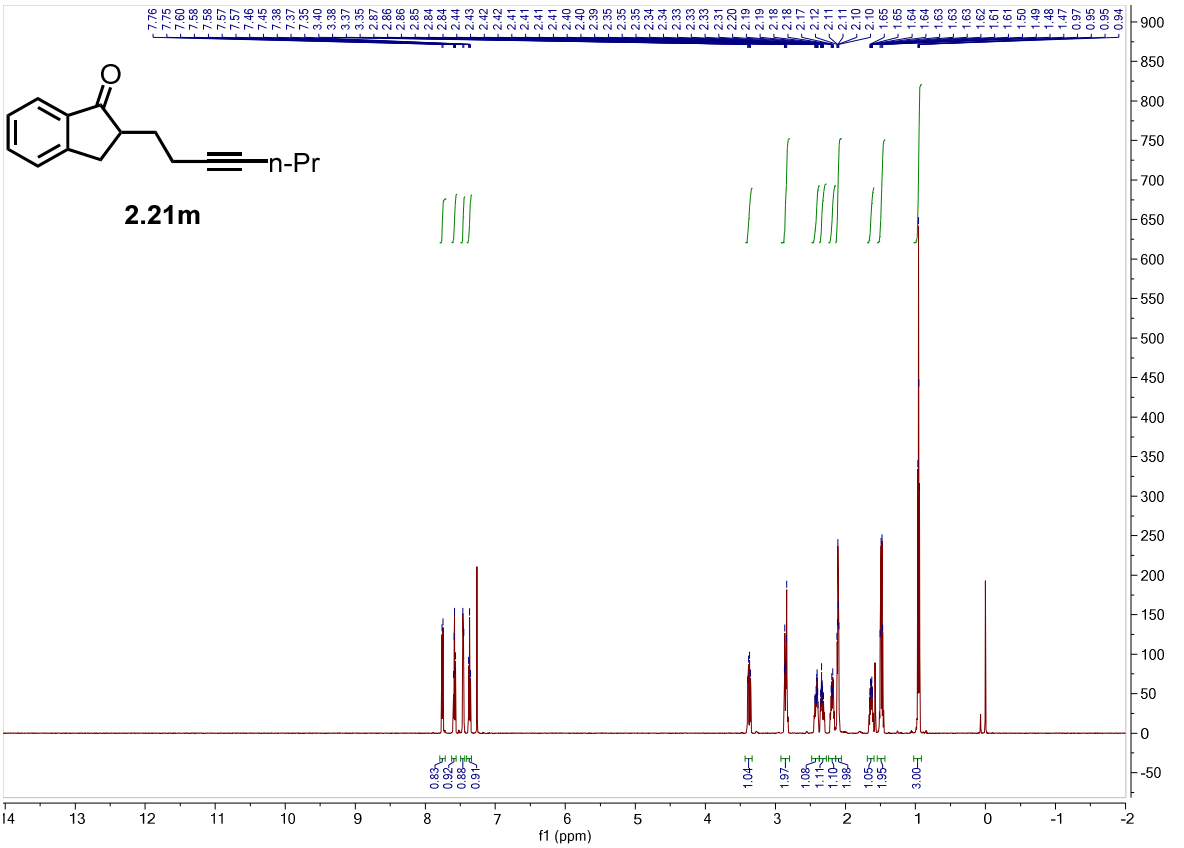
f1 (ppm)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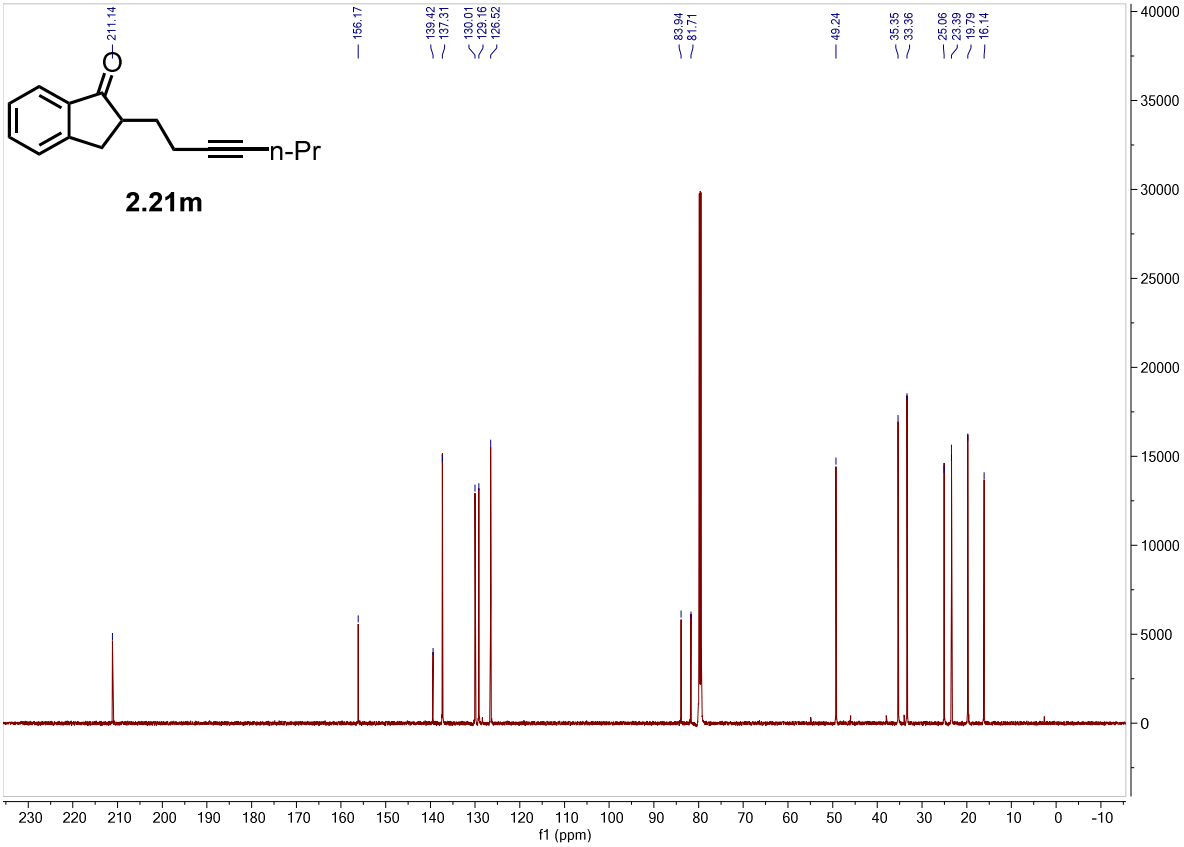
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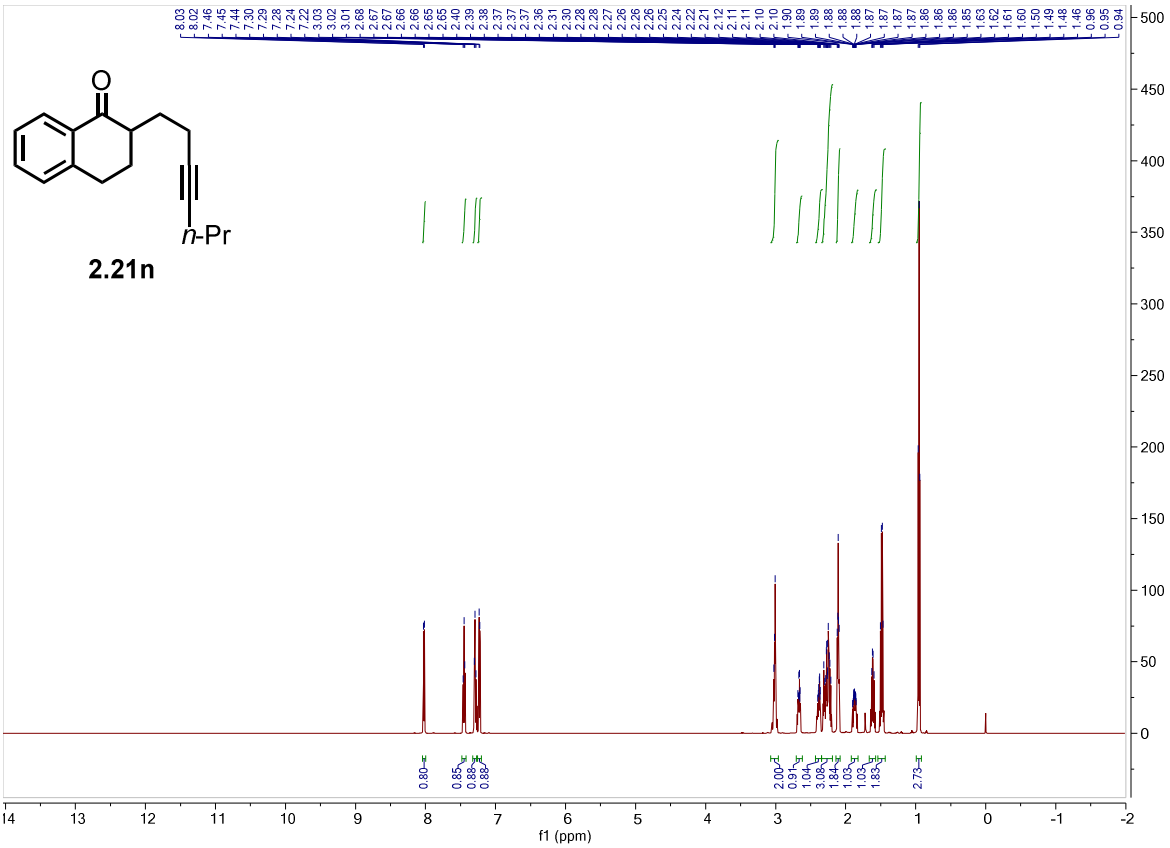
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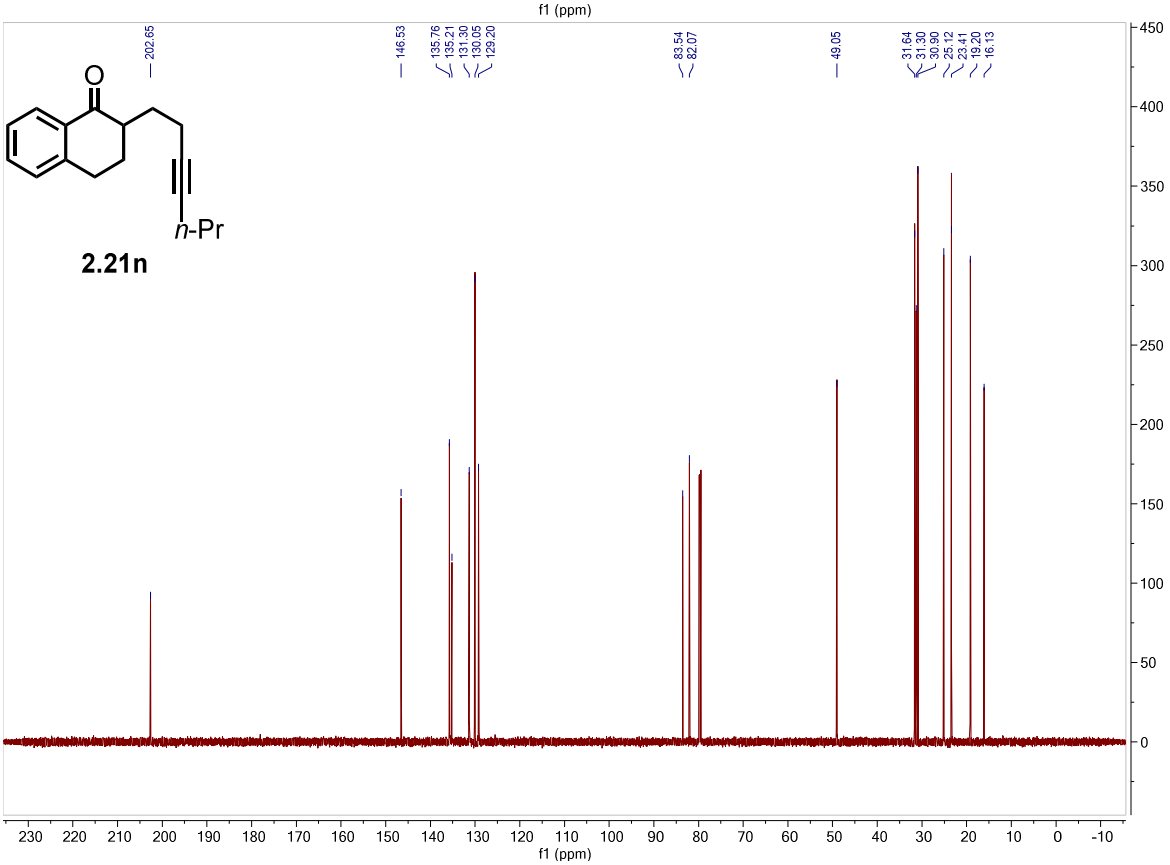
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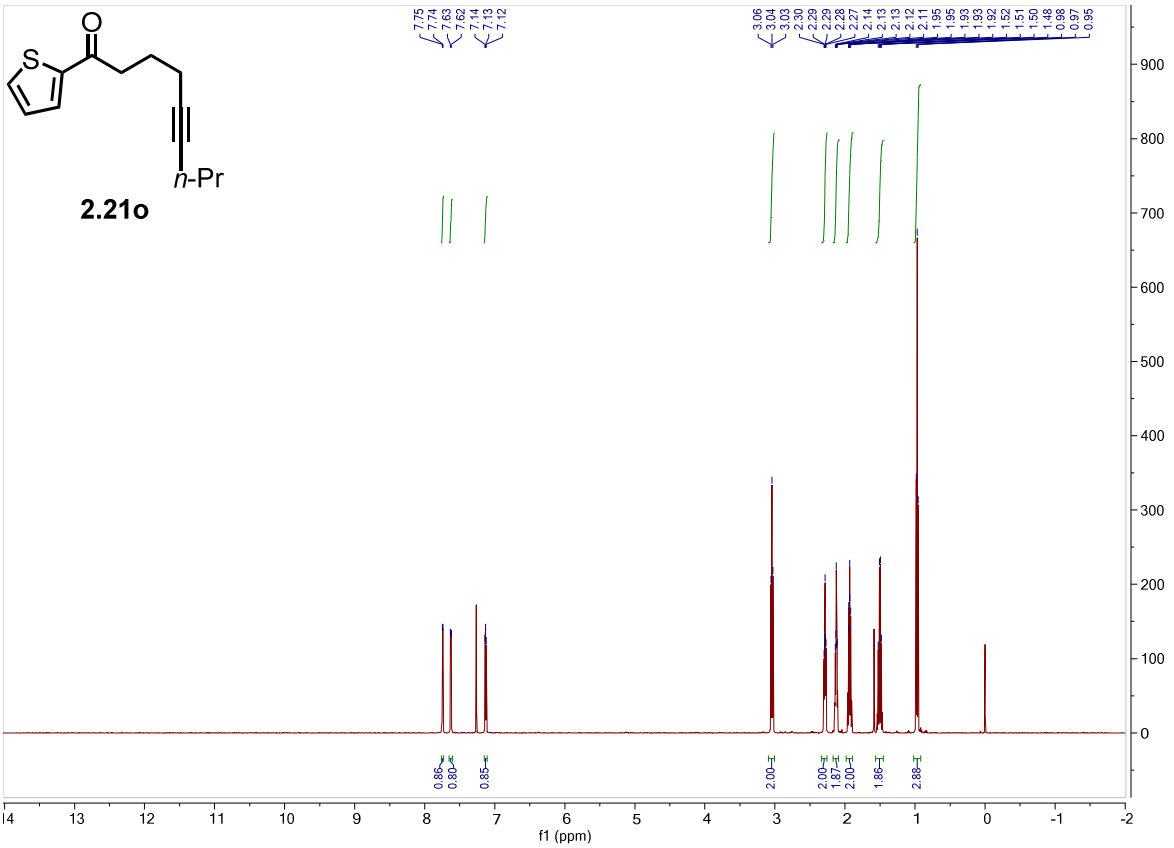
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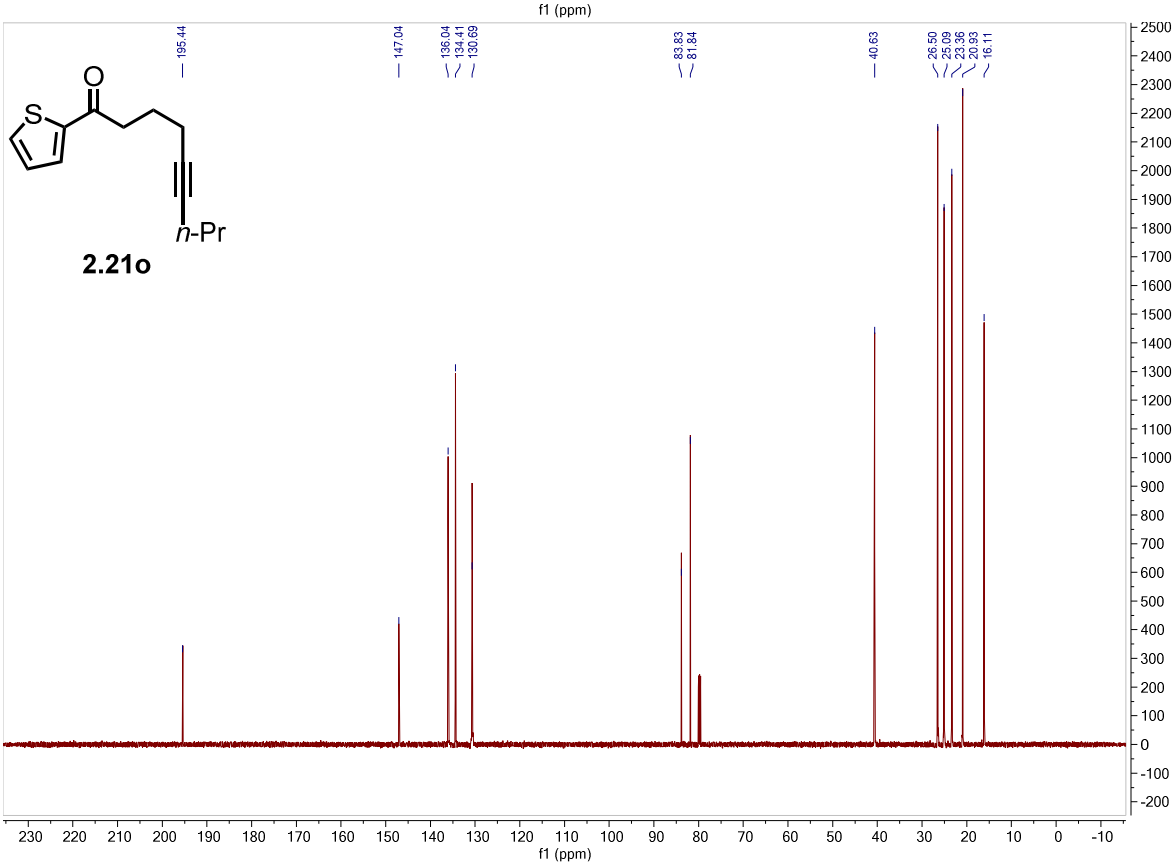
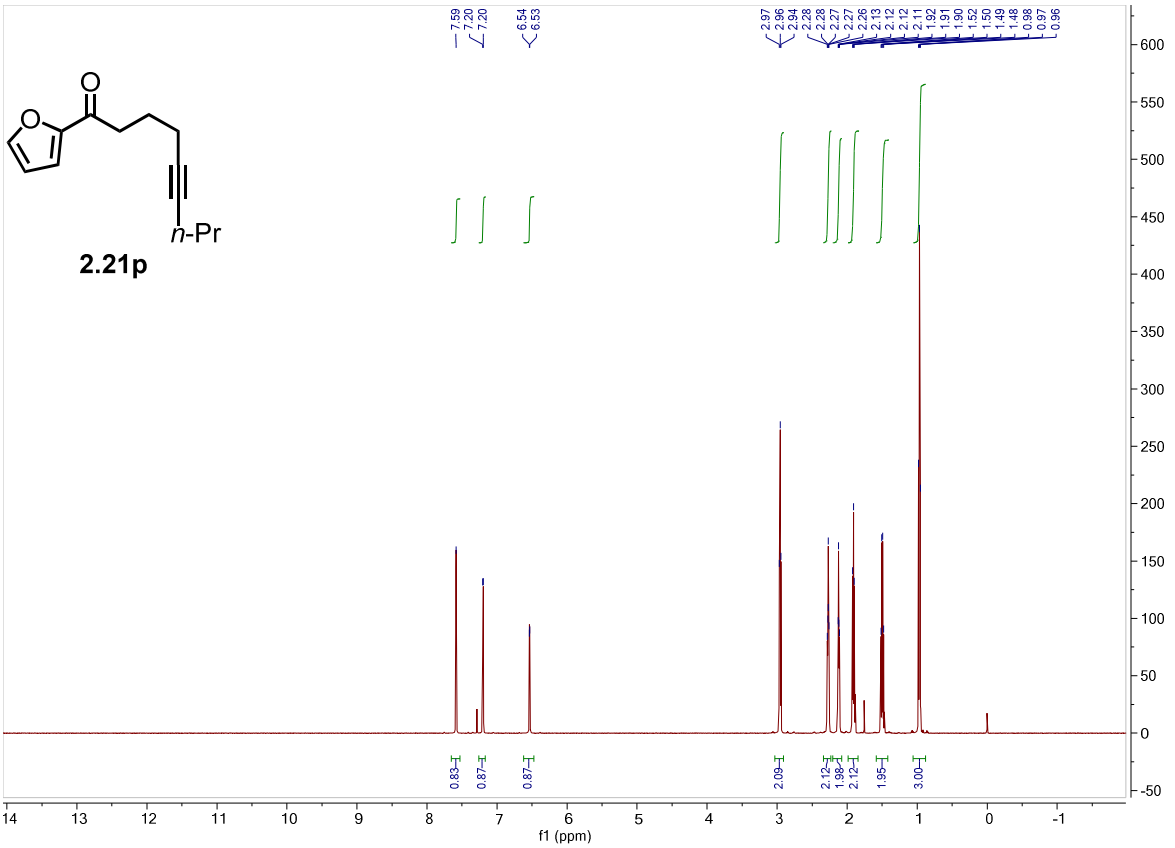
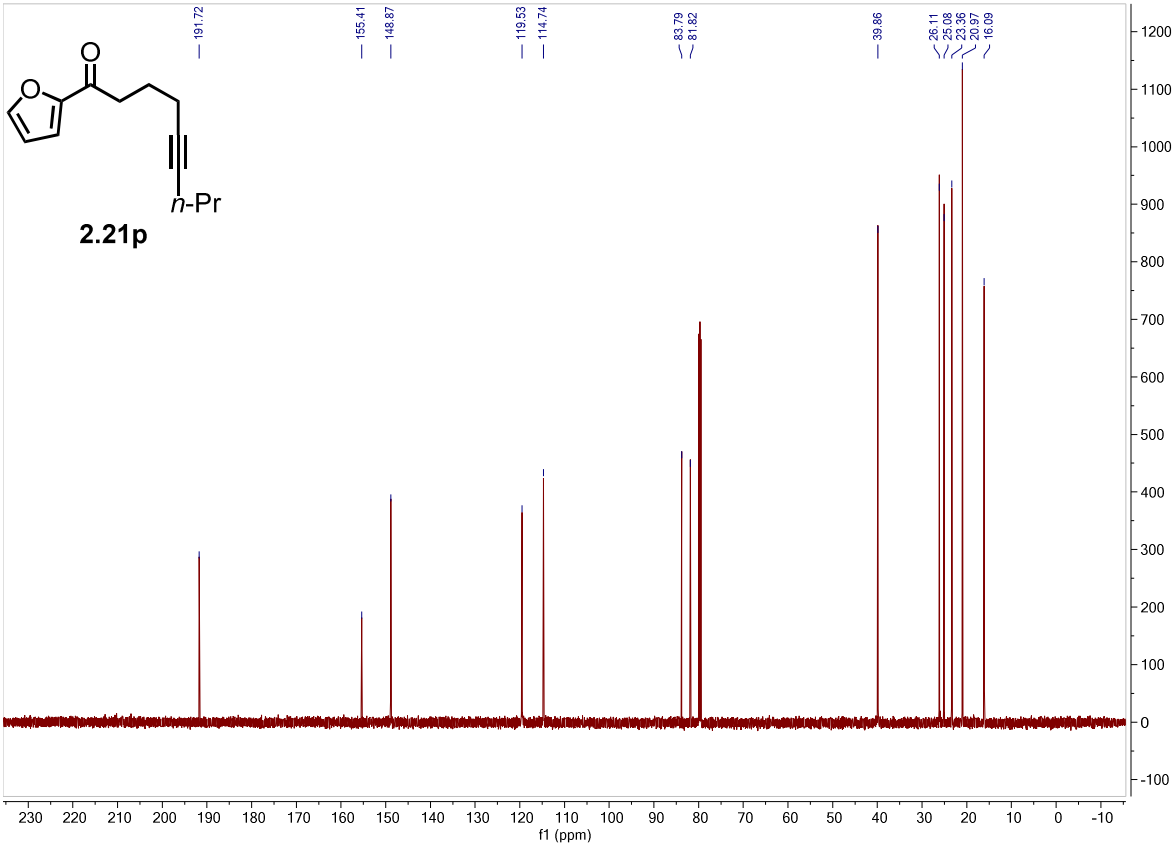
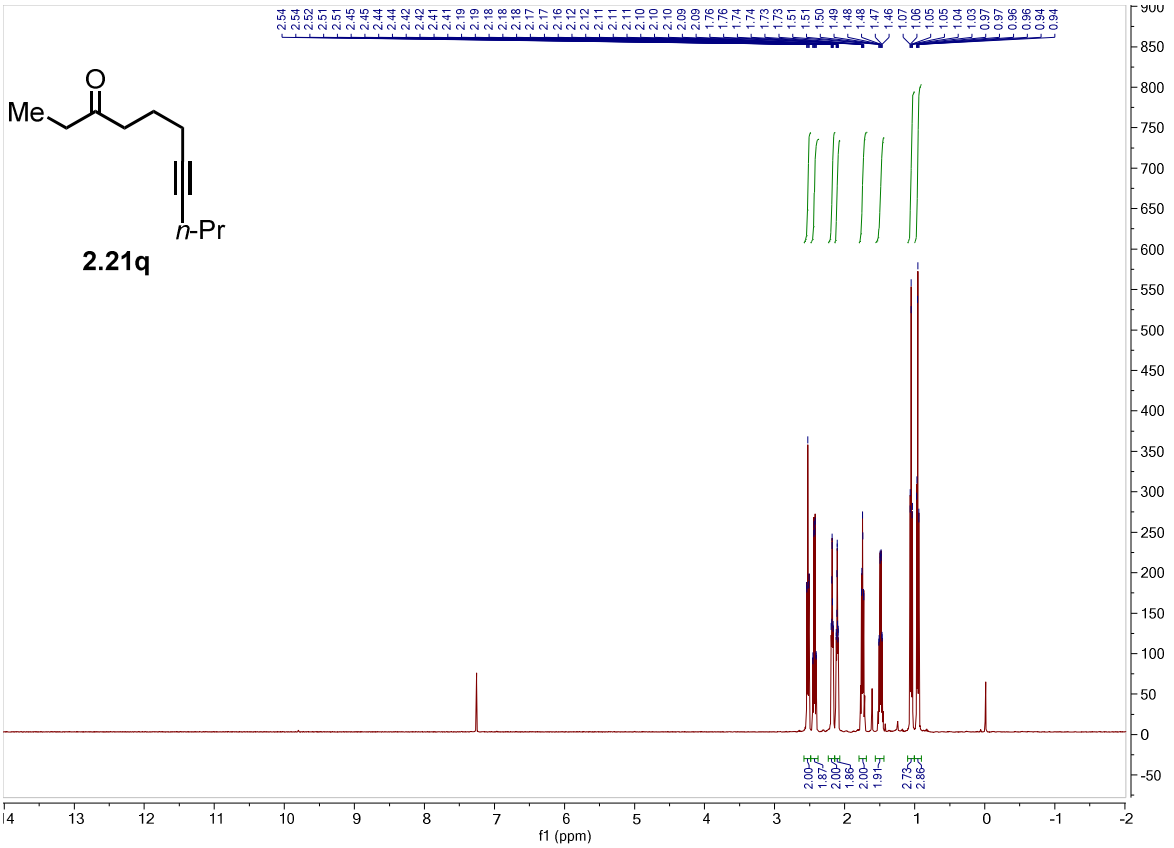
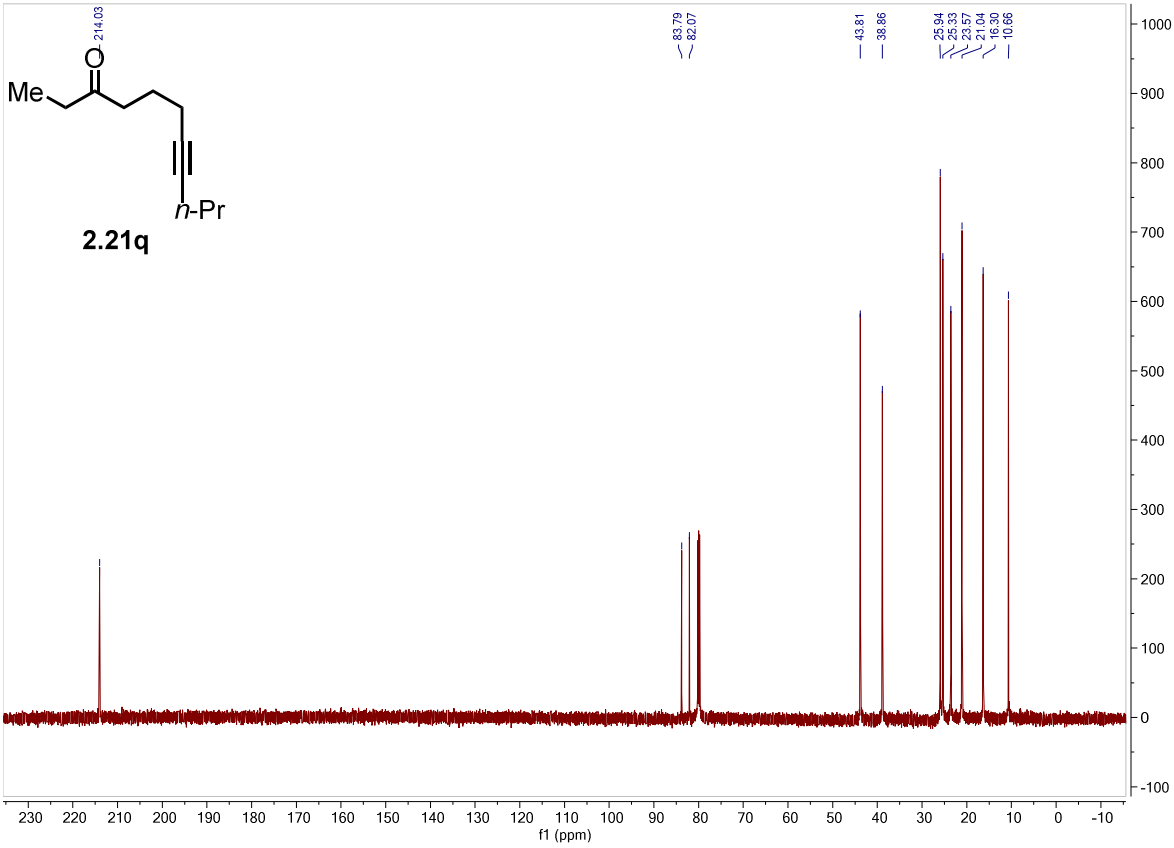
f1 (ppm)


n-Pr
2.21o
f1 (ppm)


n-Pr
2.21p
f1 (ppm)


n-Pr
2.21p
f1 (ppm)


Me
n-Pr
2.21q
f1 (ppm)


214.03
83.79
82.07
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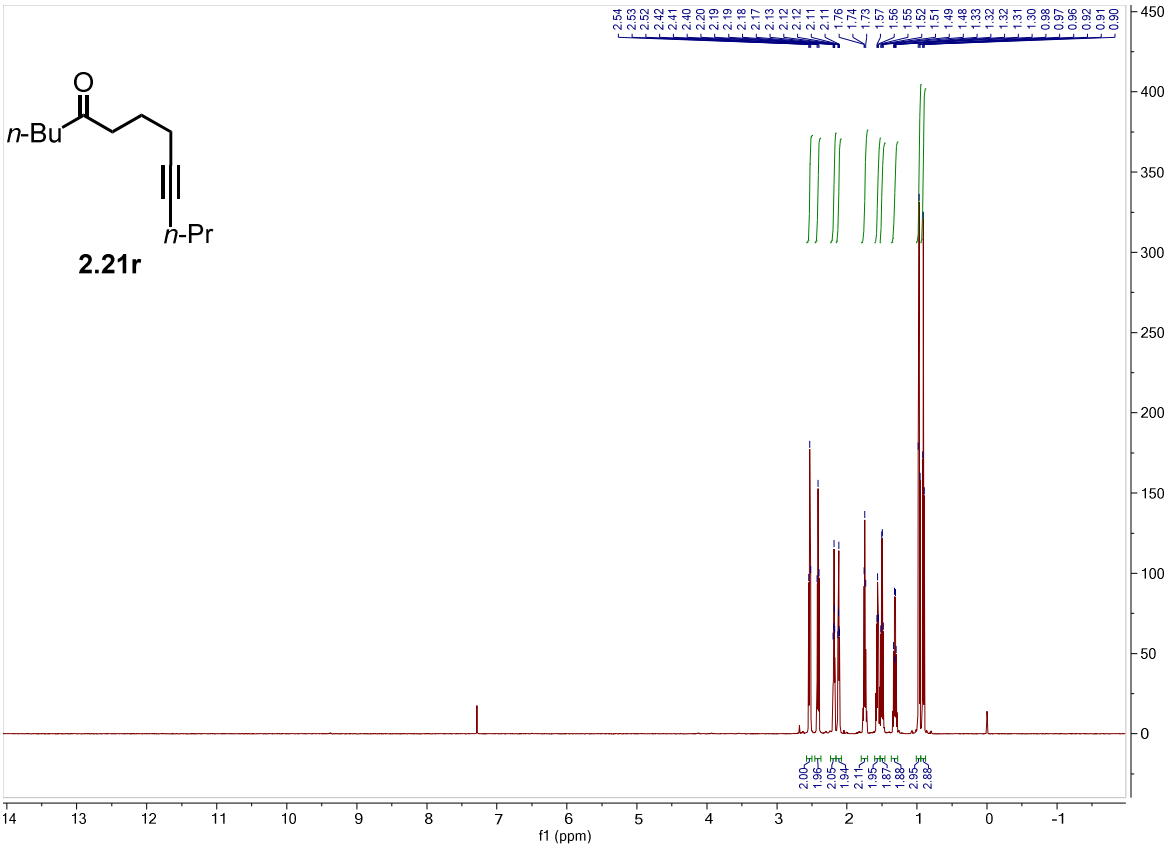
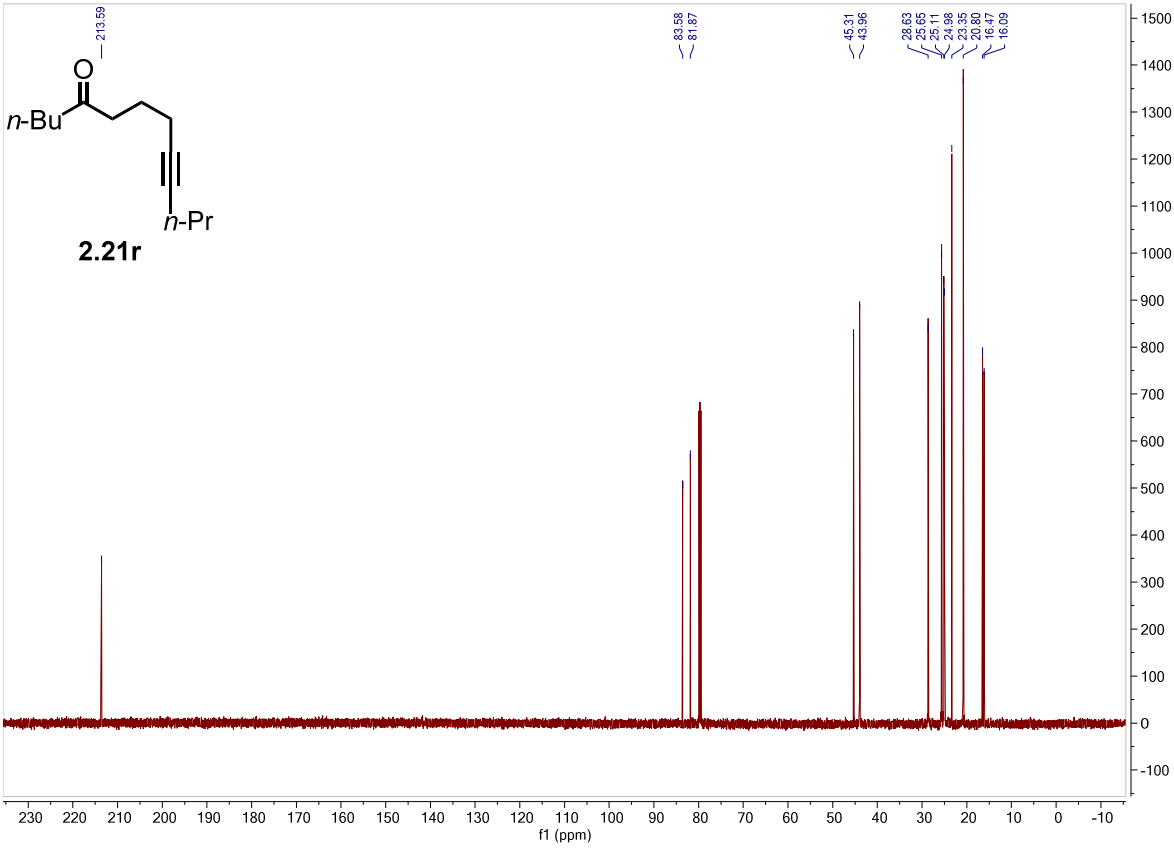
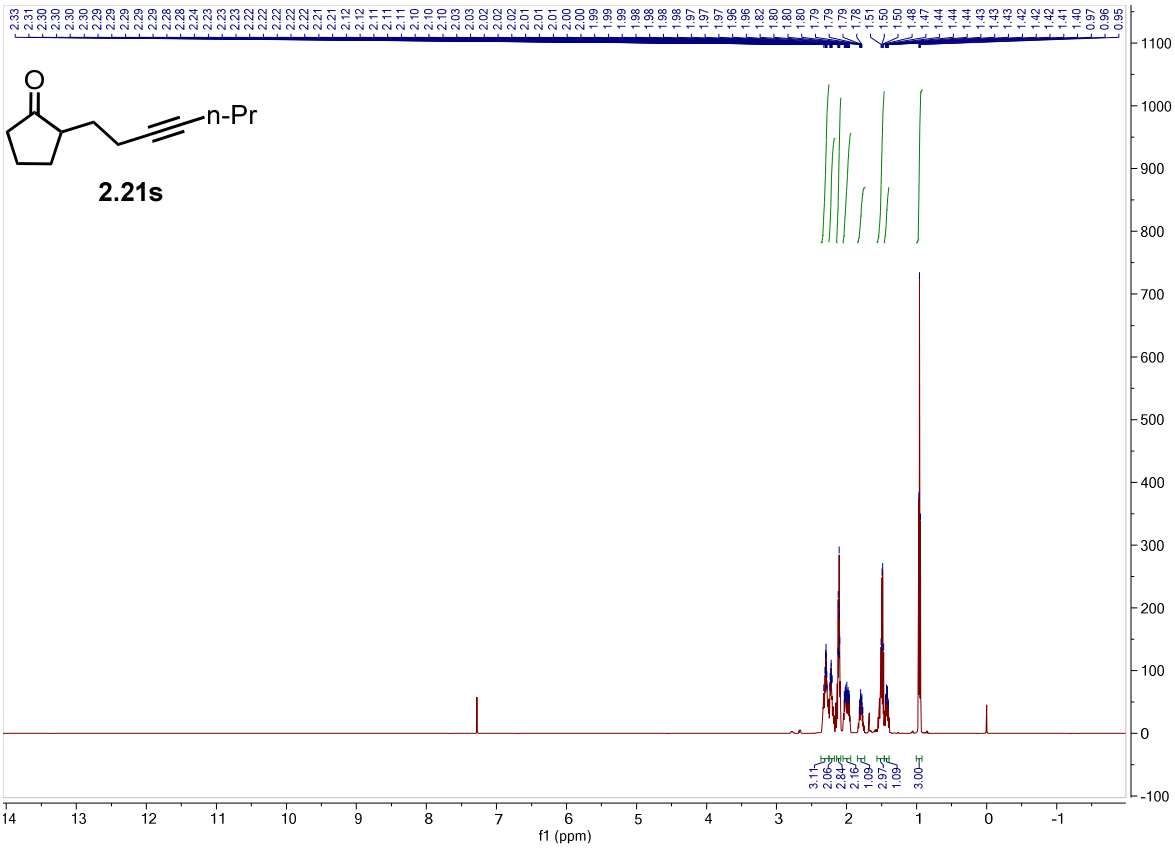
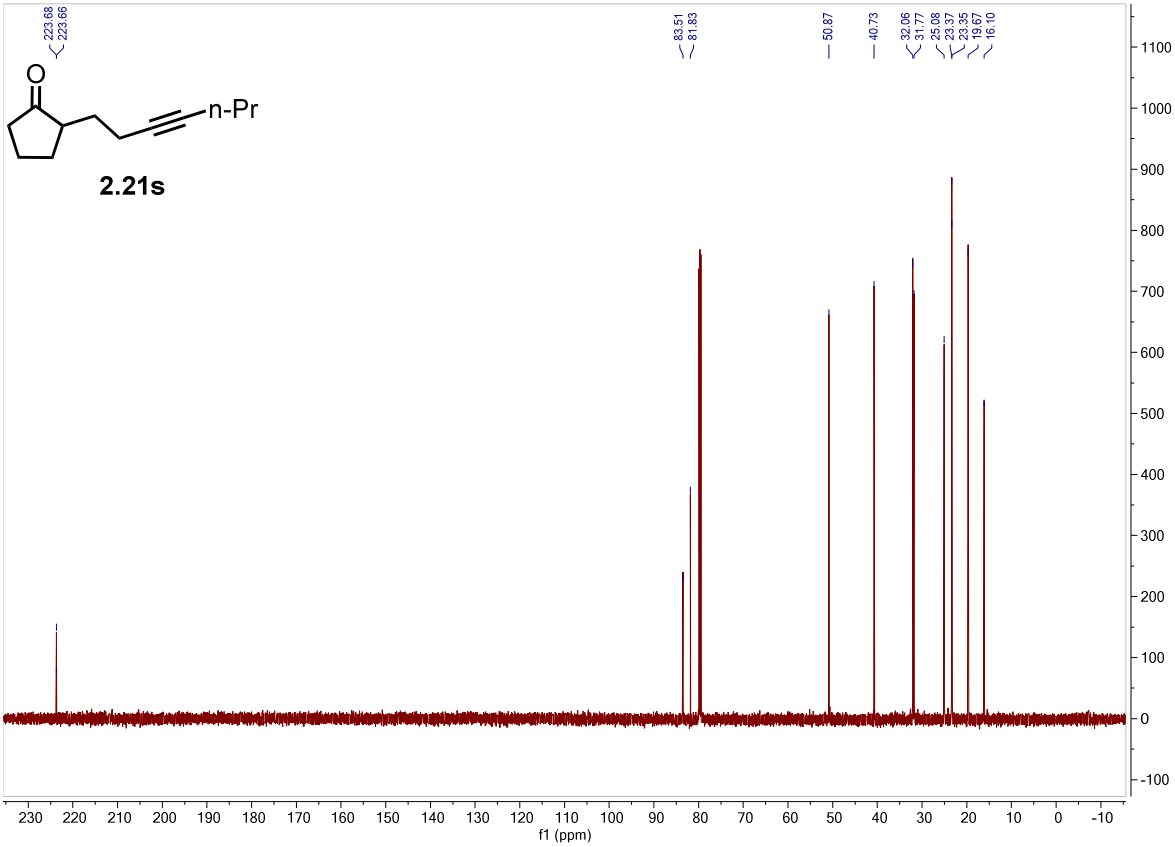
25.33
23.57
21.04
16.30
10.66
Me
n-Pr
2.21q
f1 (ppm)


n-Bu
n-Pr
2.21r
f1 (ppm)


n-Bu
n-Pr
2.21r
213.59
83.58
81.87
45.31
43.96
28.63
25.65
25.11
24.98
23.35
20.80
16.47
16.09
f1 (ppm)


n-Pr
2.21s
f1 (ppm)


223.68
223.66
83.51
81.83
50.87
40.73
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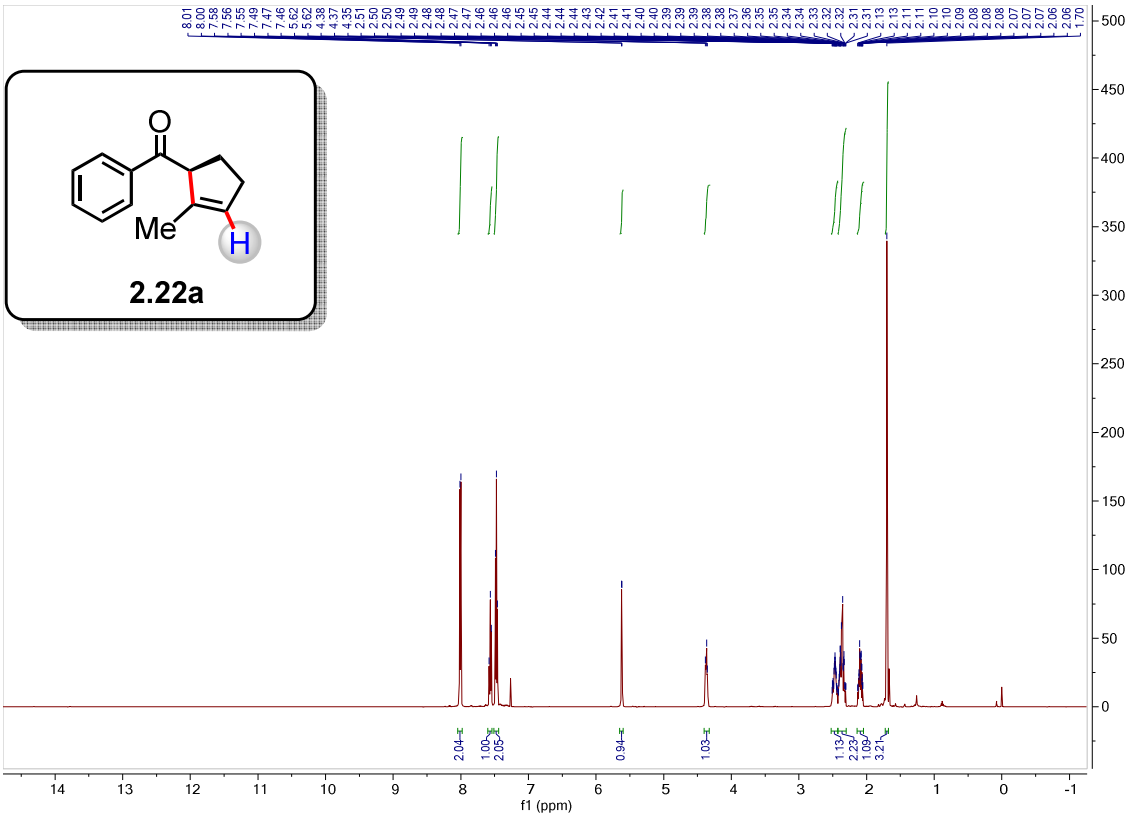
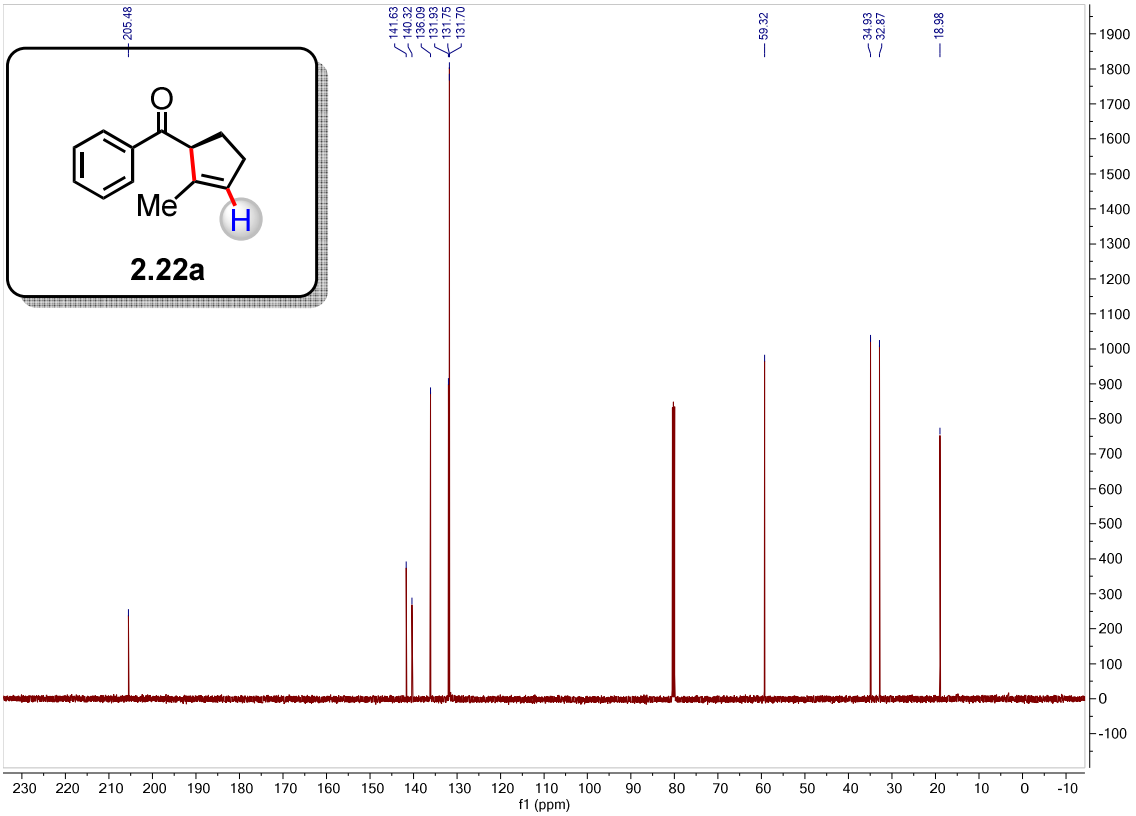
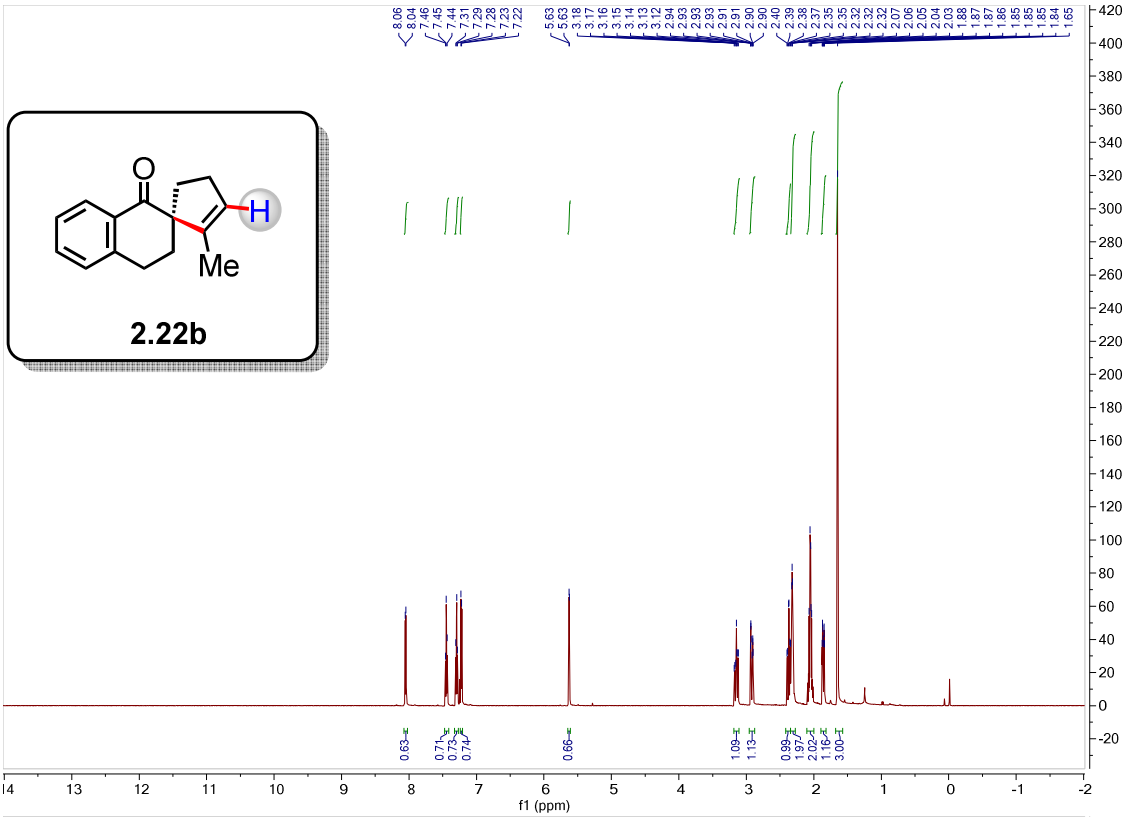
31.77
25.08
23.37
23.35
19.67
16.10
n-Pr
2.21s
f1 (ppm)


O
Me
H
2.22a
f1 (ppm)


O
Me
H
2.22a
205.48
141.63
140.32
136.09
131.93
131.75
131.70
59.32
34.93
32.87
18.98
f1 (ppm)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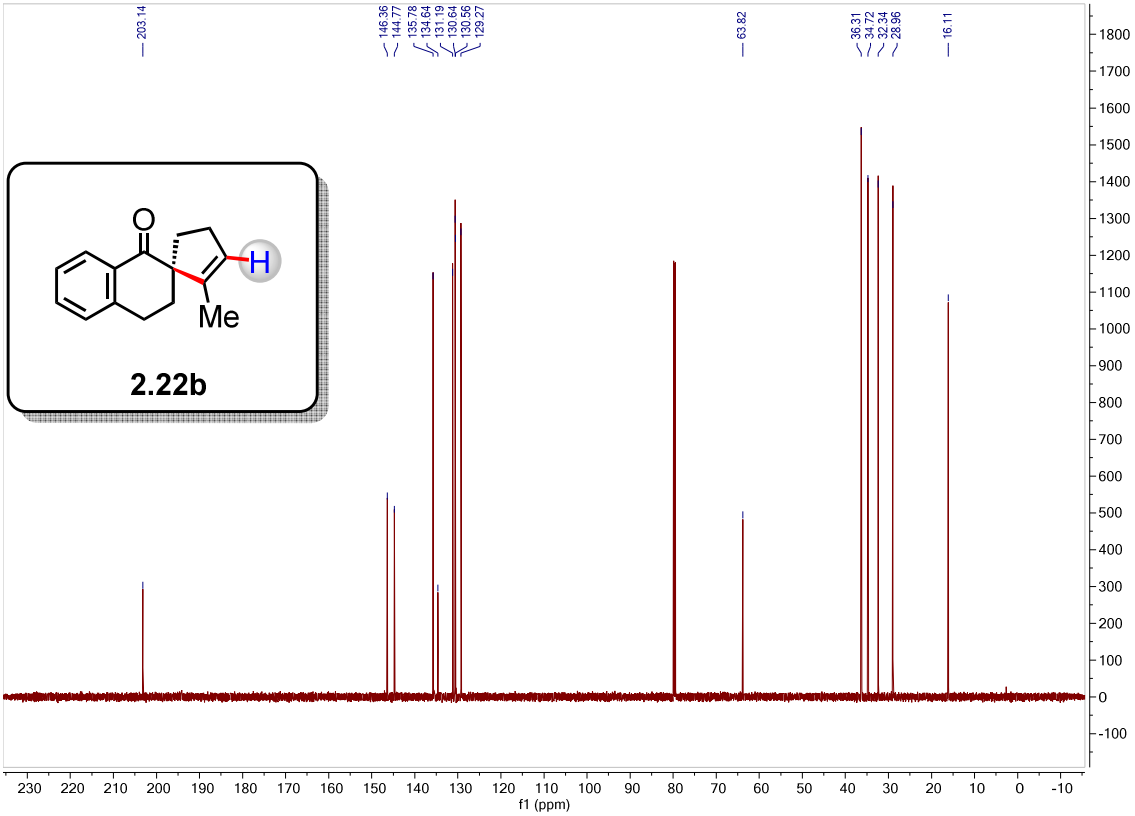
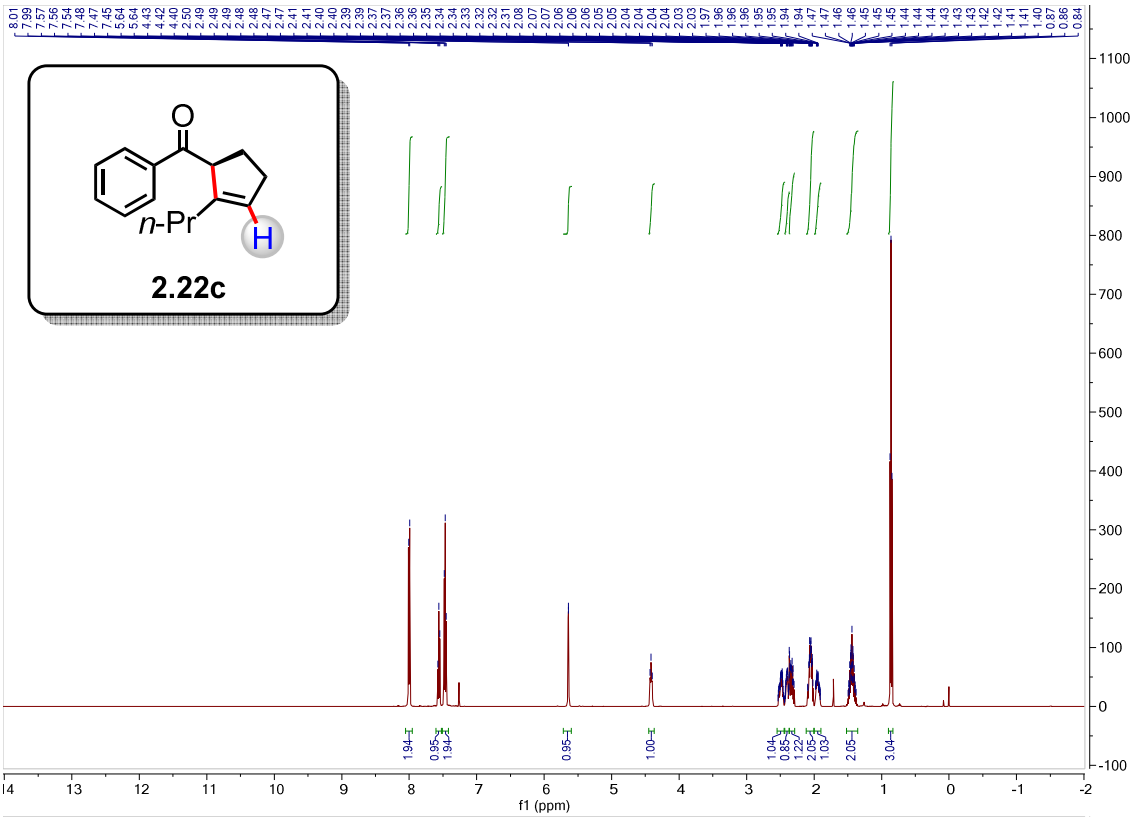
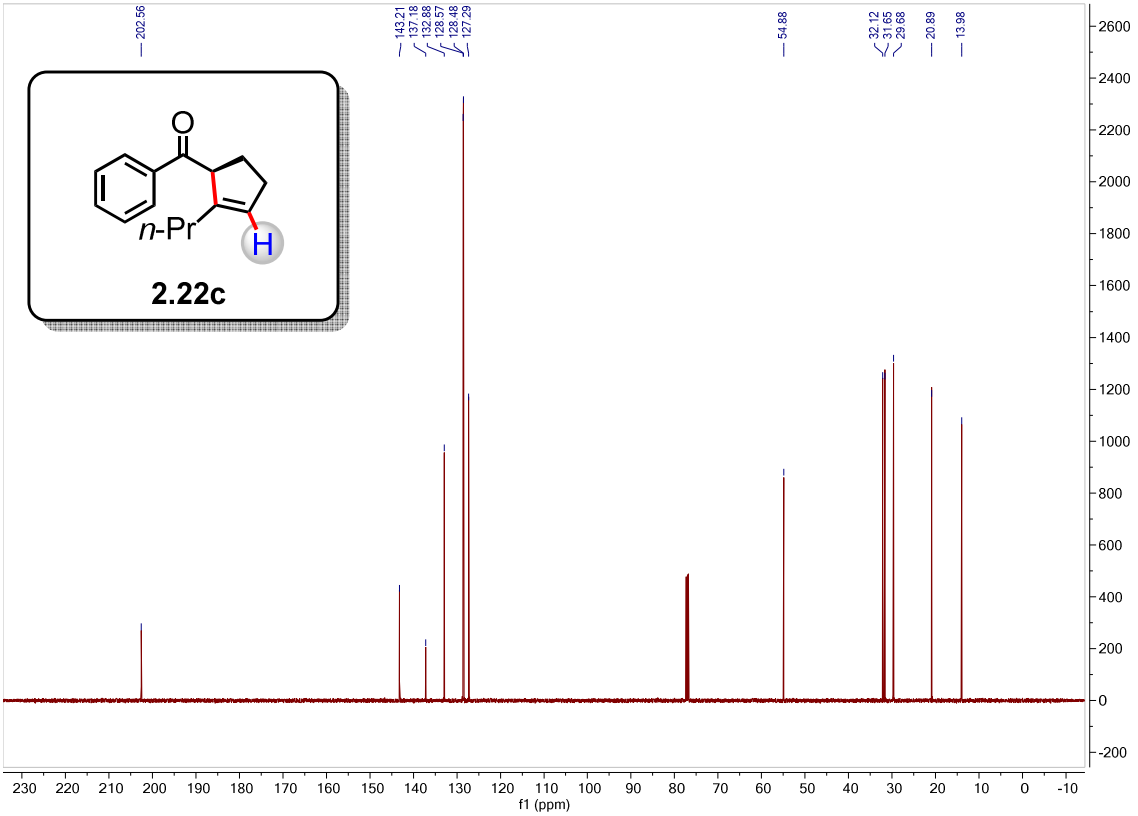
H
Me
2.22b
f1 (ppm)


O
H
Me
2.22b
f1 (ppm)


O
n-Pr
H
2.22c
f1 (ppm)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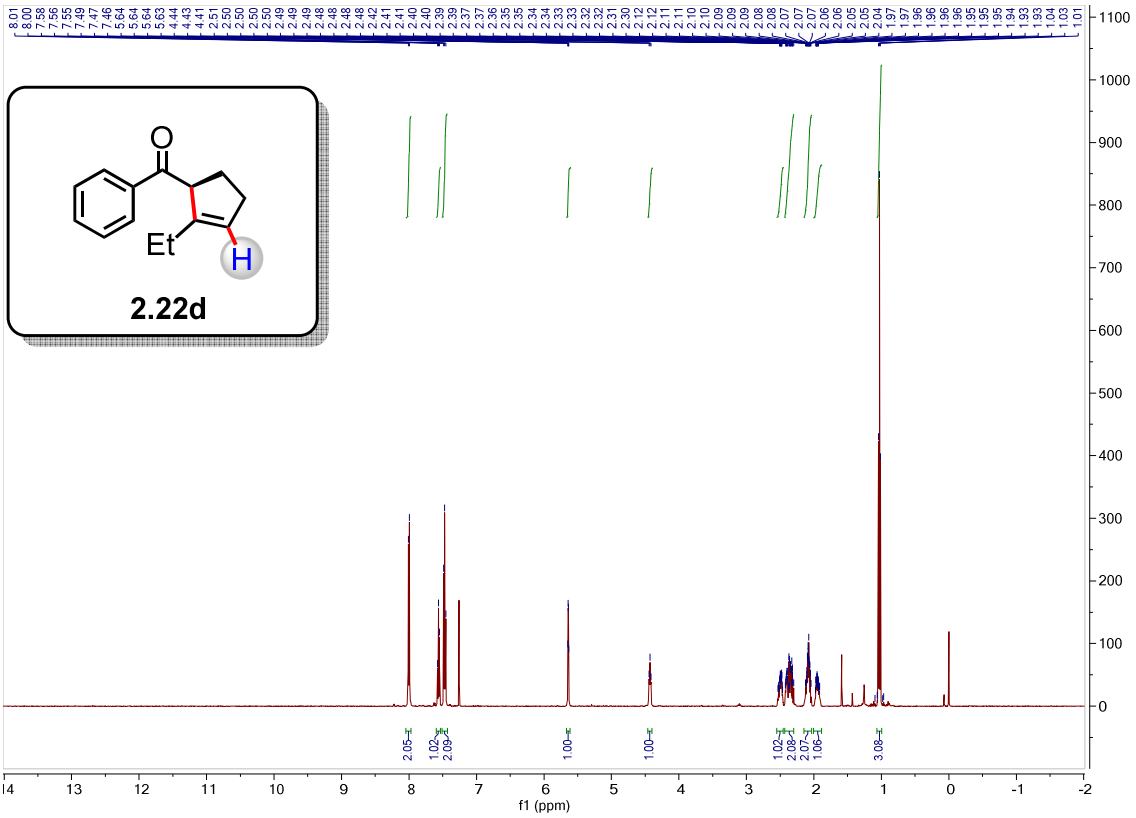
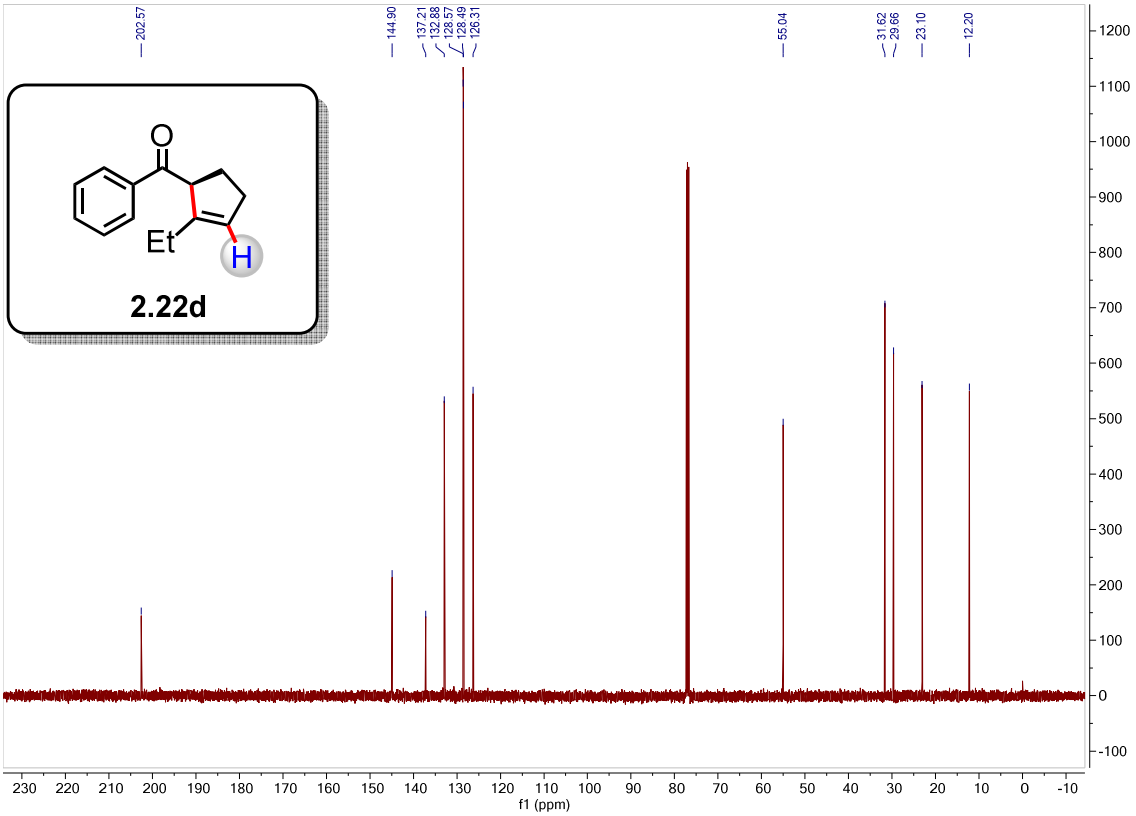
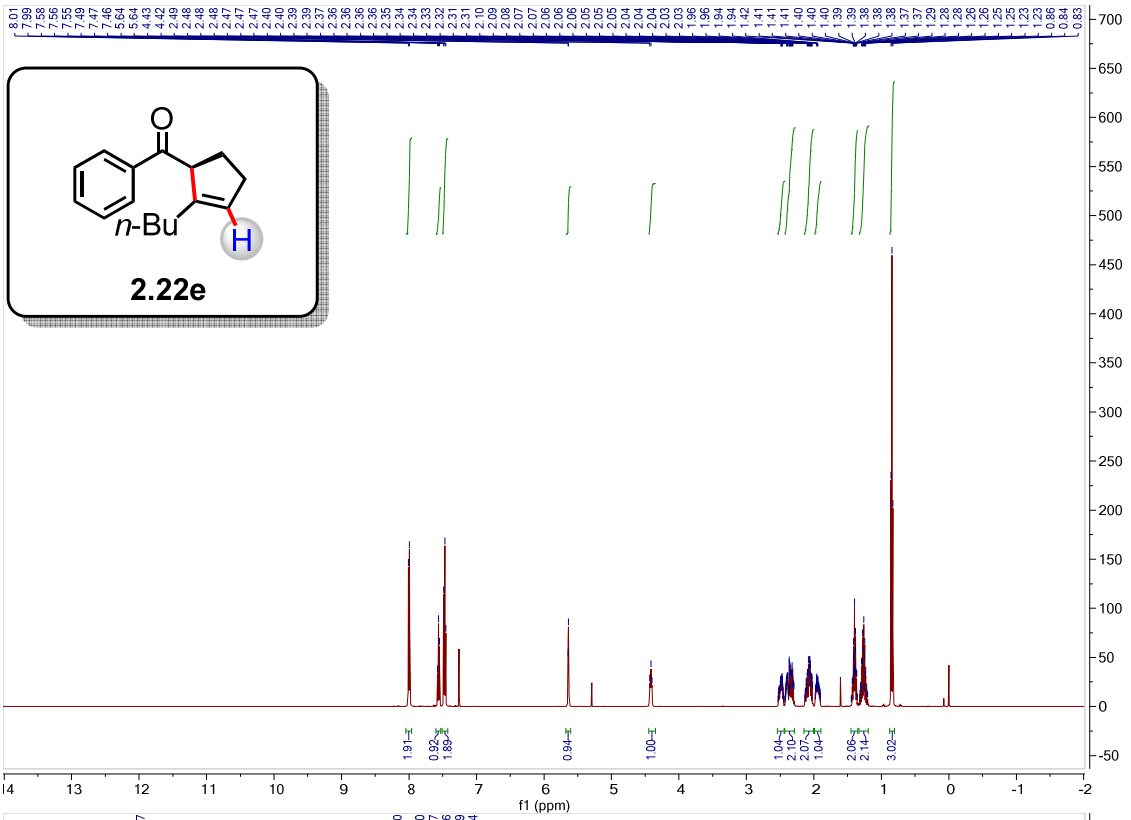
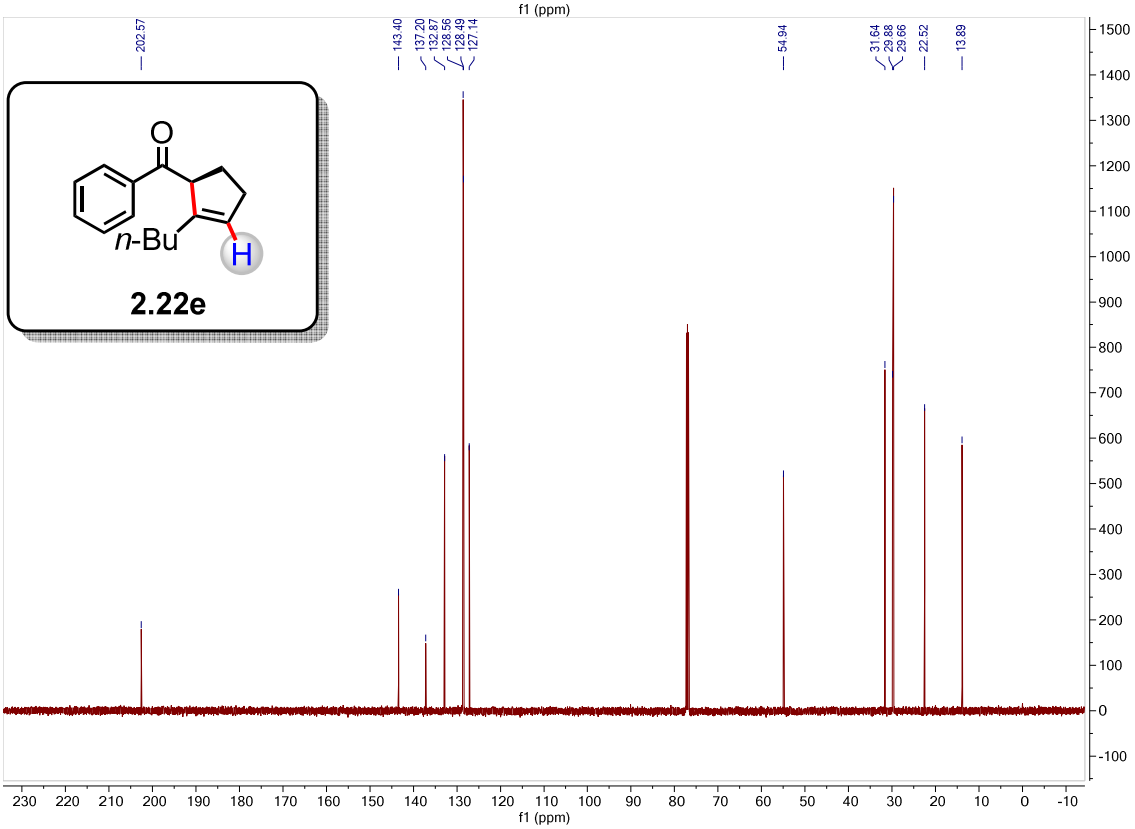
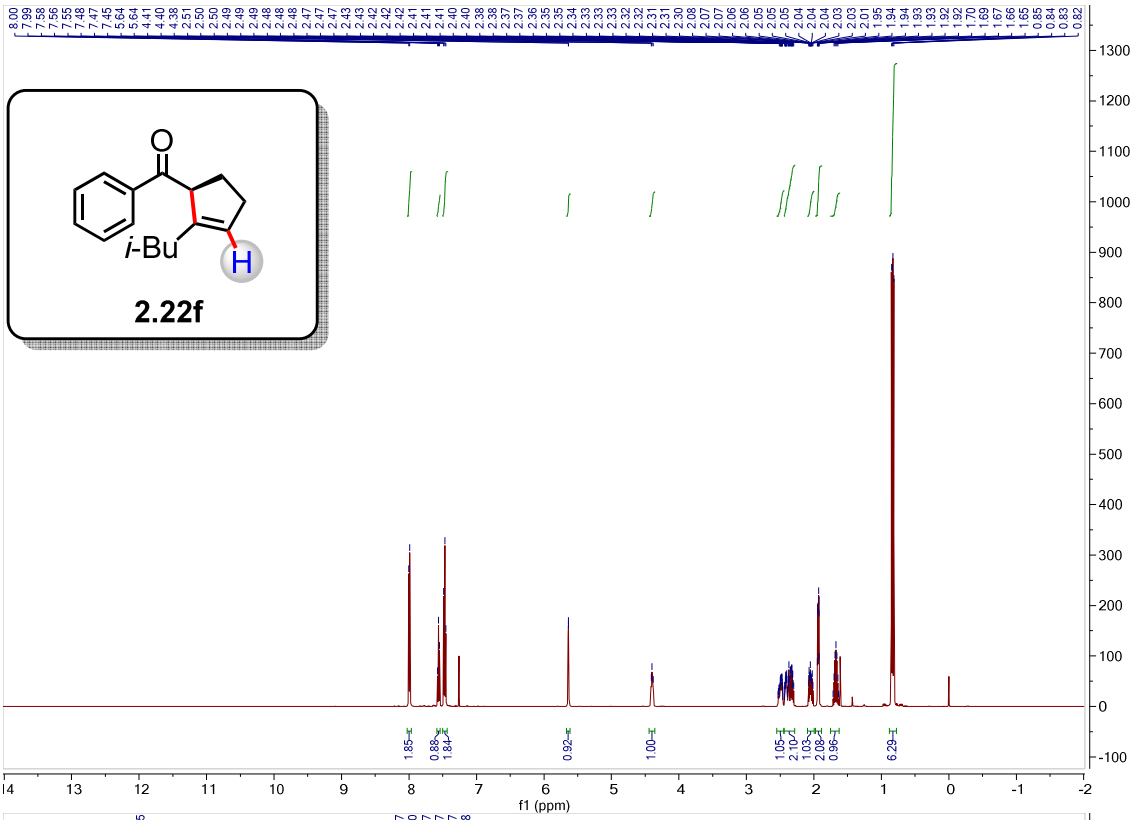
143.21
137.18
132.88
128.57
128.48
127.29
54.88
32.12
31.65
29.68
20.89
13.98
O
n-Pr
H
2.22c
f1 (ppm)

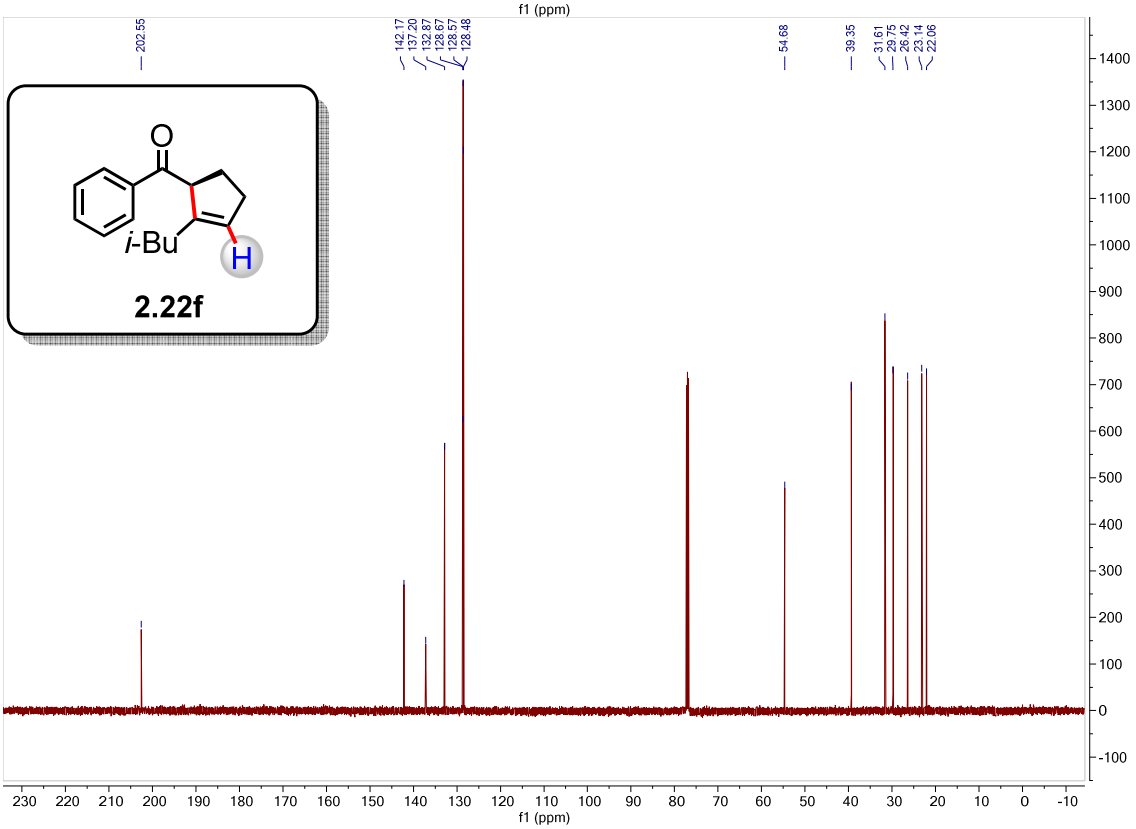

O
Et
H
2.22d
f1 (ppm)

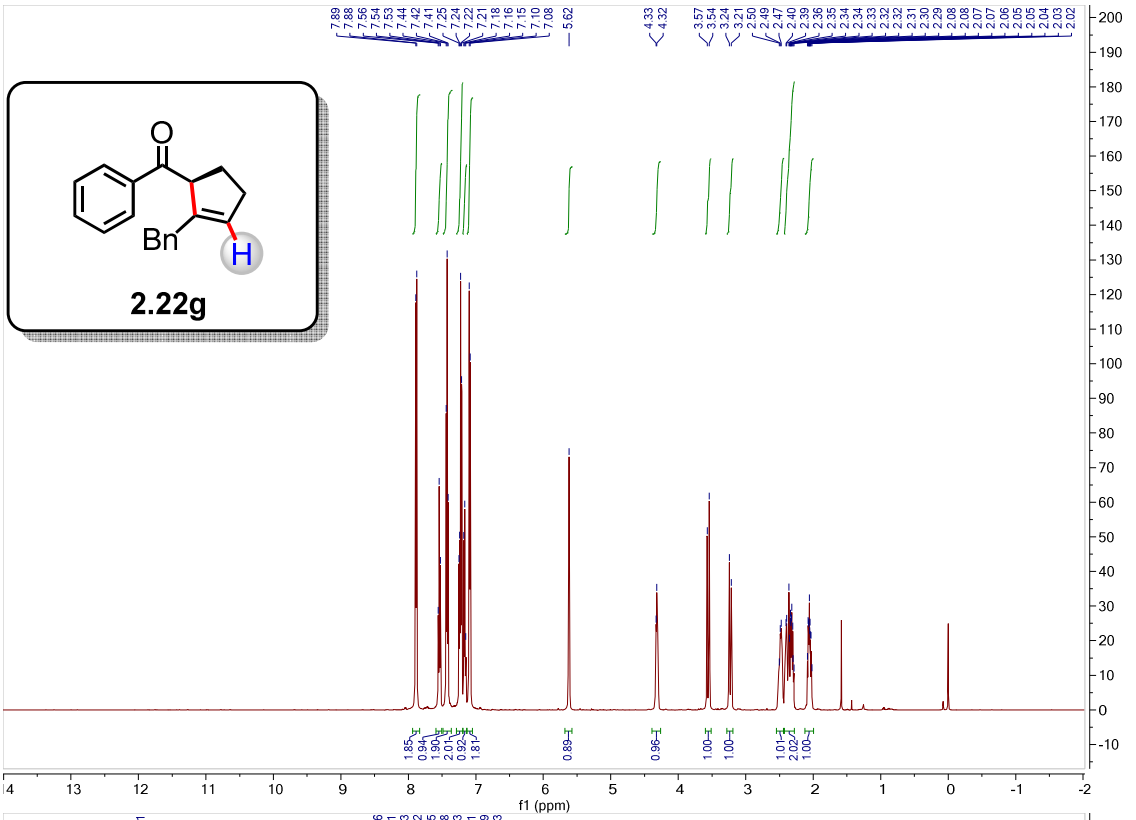

O
Et
H
2.22d
f1 (ppm)

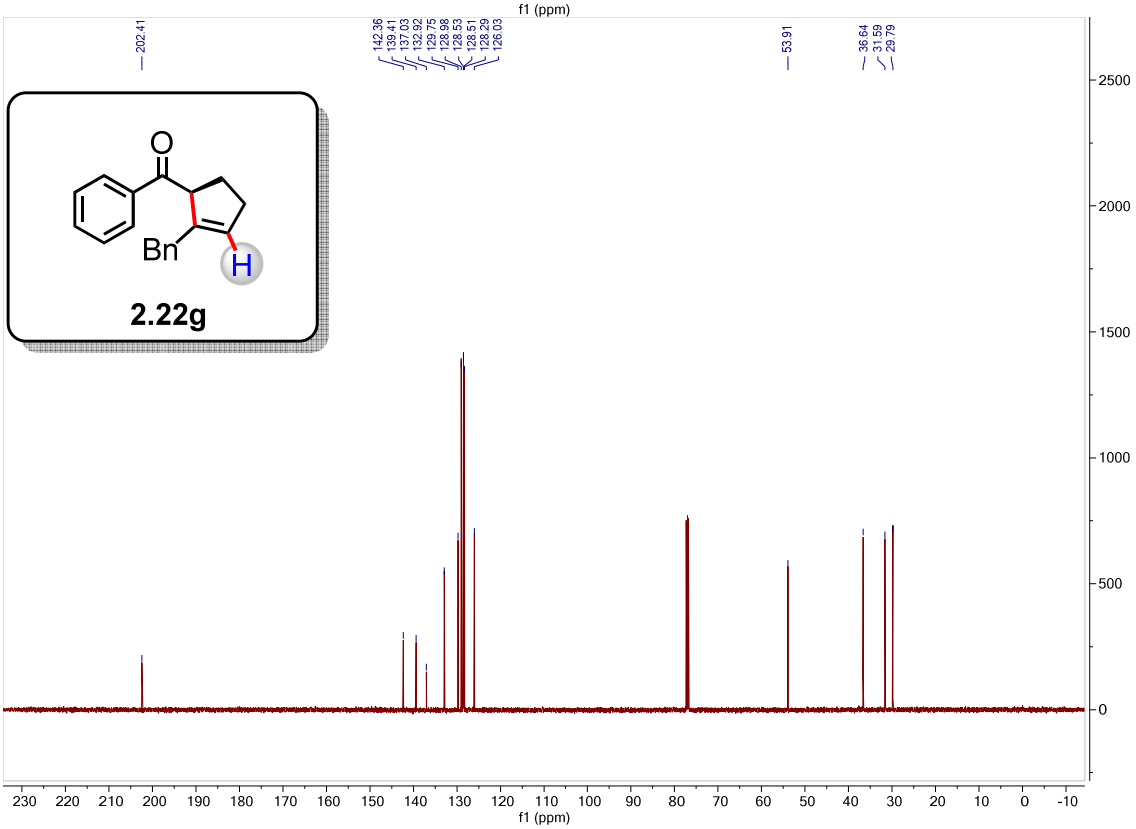

n-Bu
H
2.22e
f1 (ppm)


n-Bu
H
2.22e
f1 (ppm)


i-Bu
H
2.22f
f1 (ppm)


i-Bu
H
2.22f
f1 (ppm)


O
Bn
H
2.22g
f1 (ppm)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Bn
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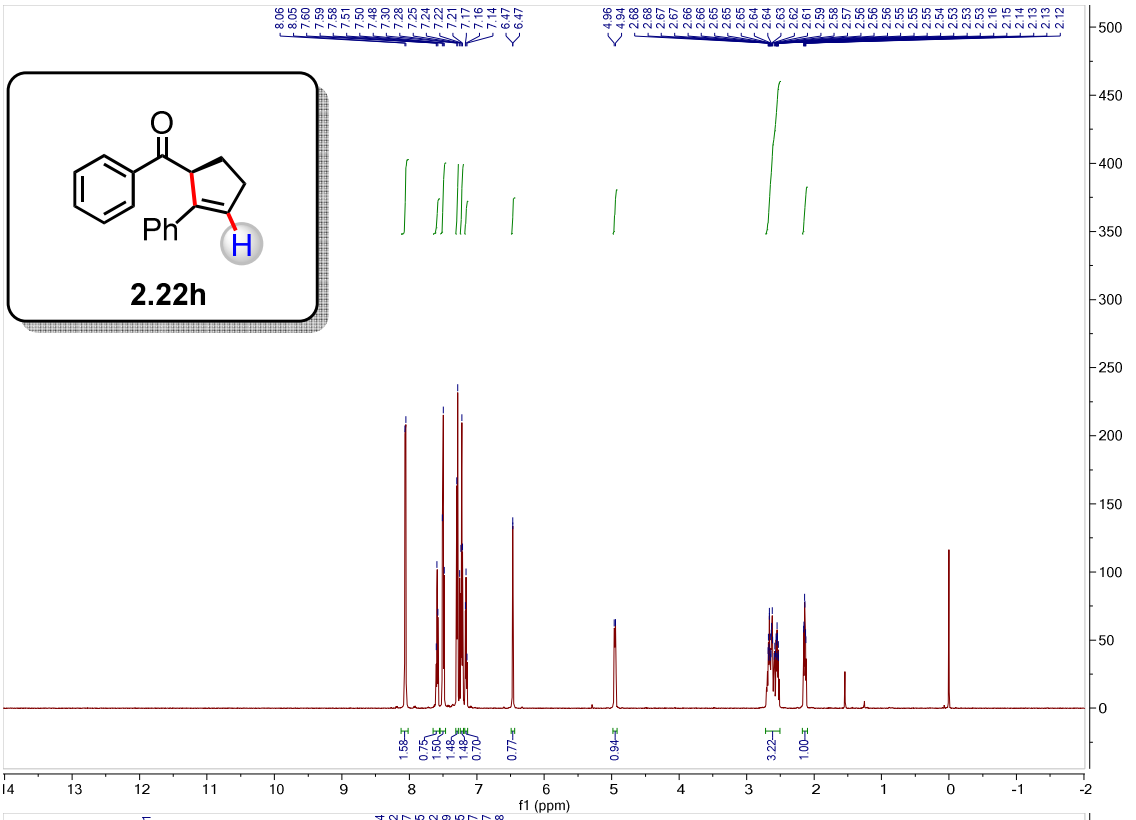
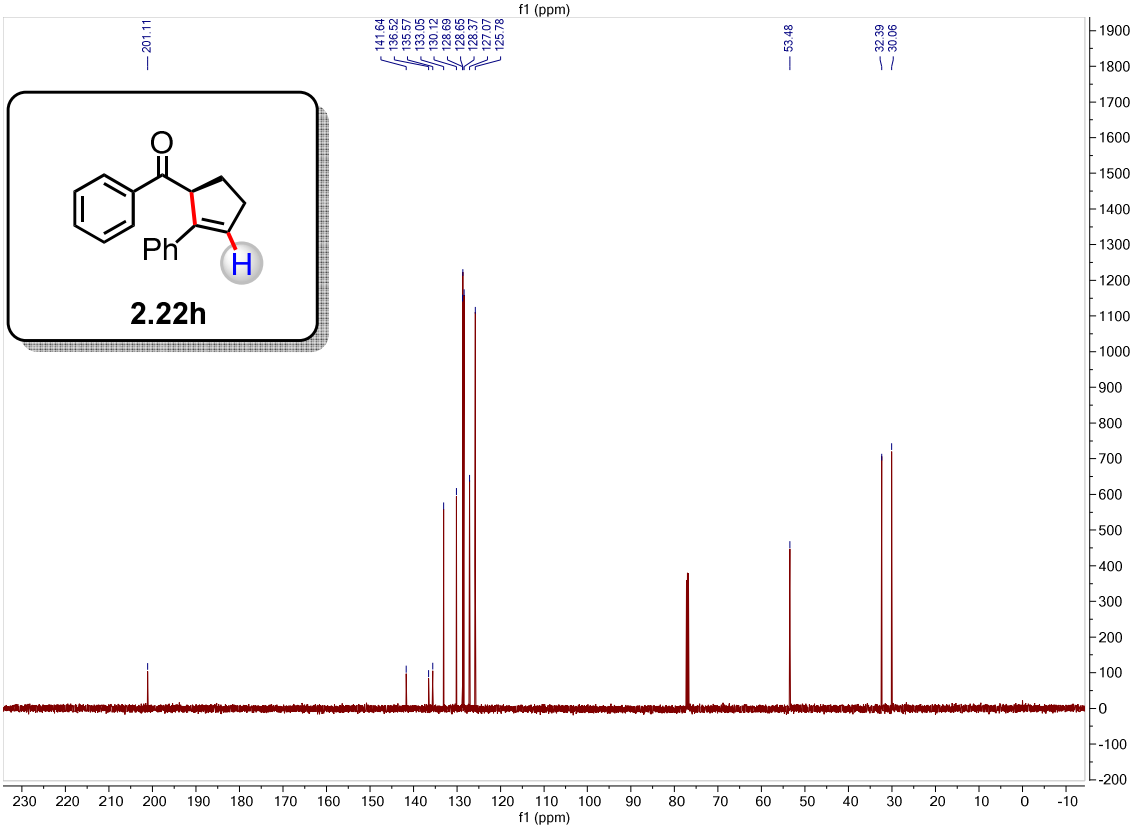
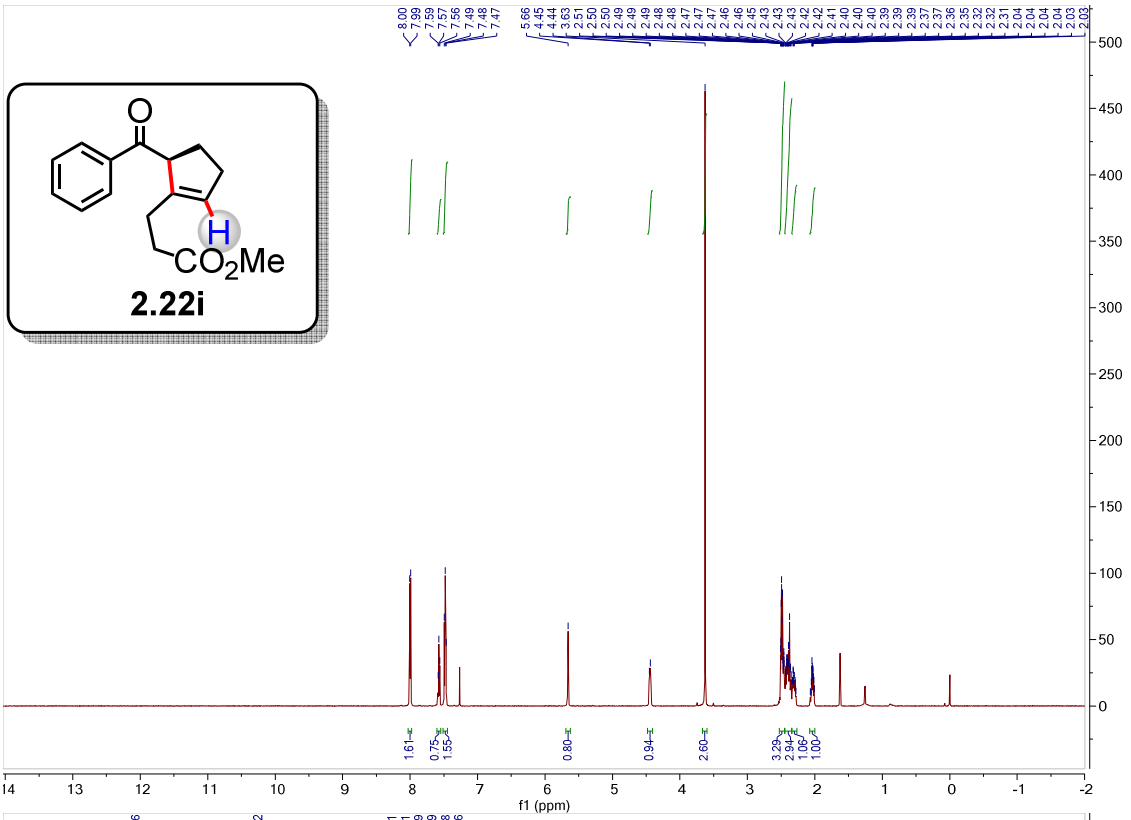
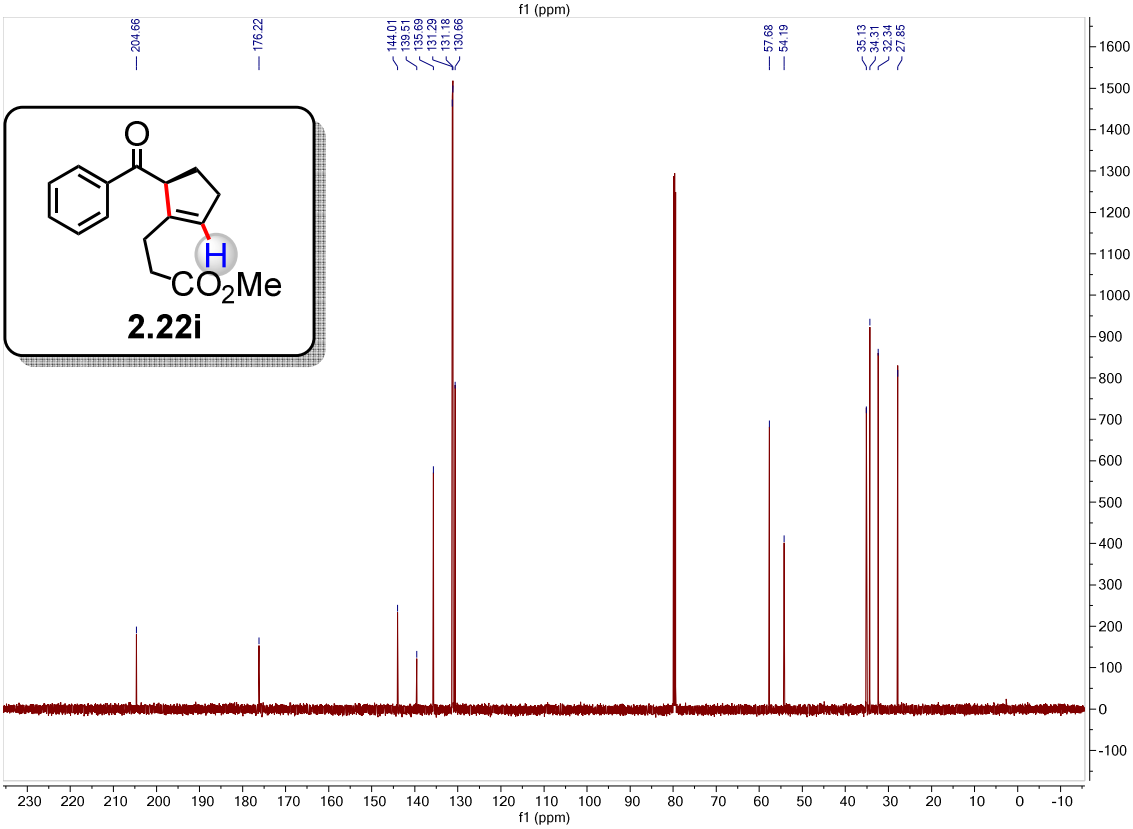
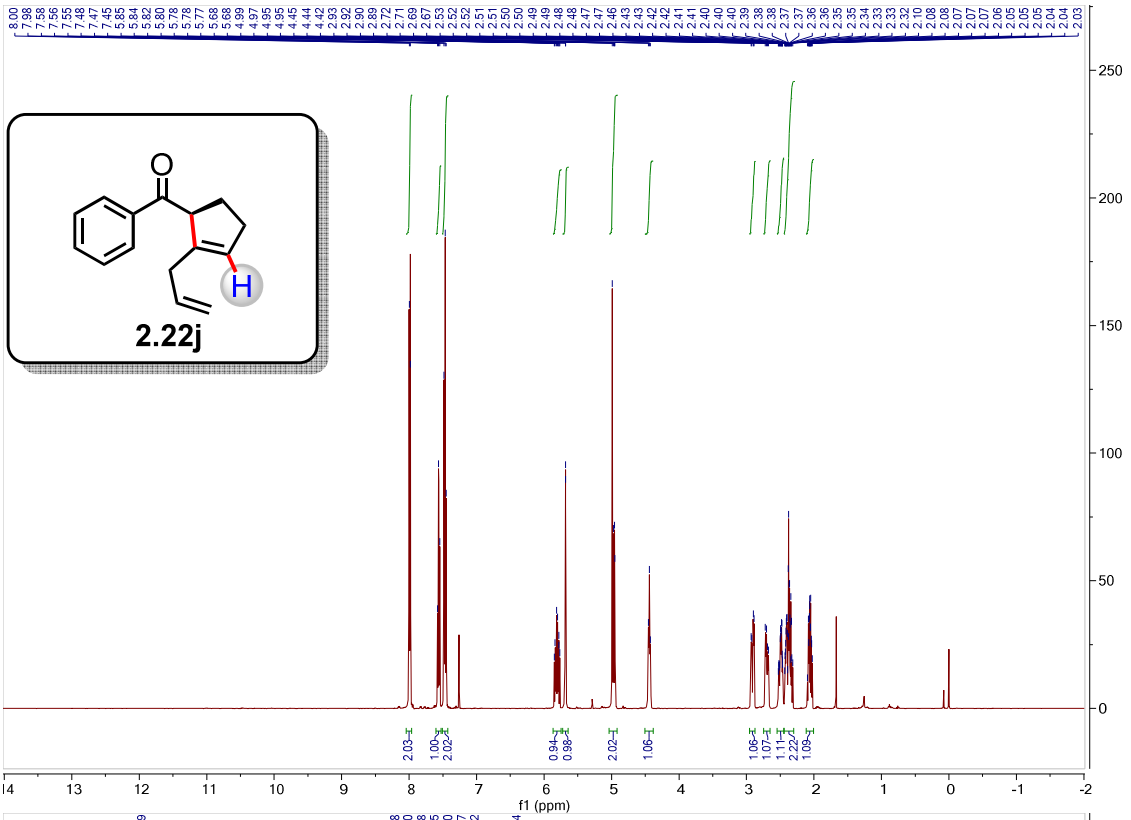
f1 (ppm)

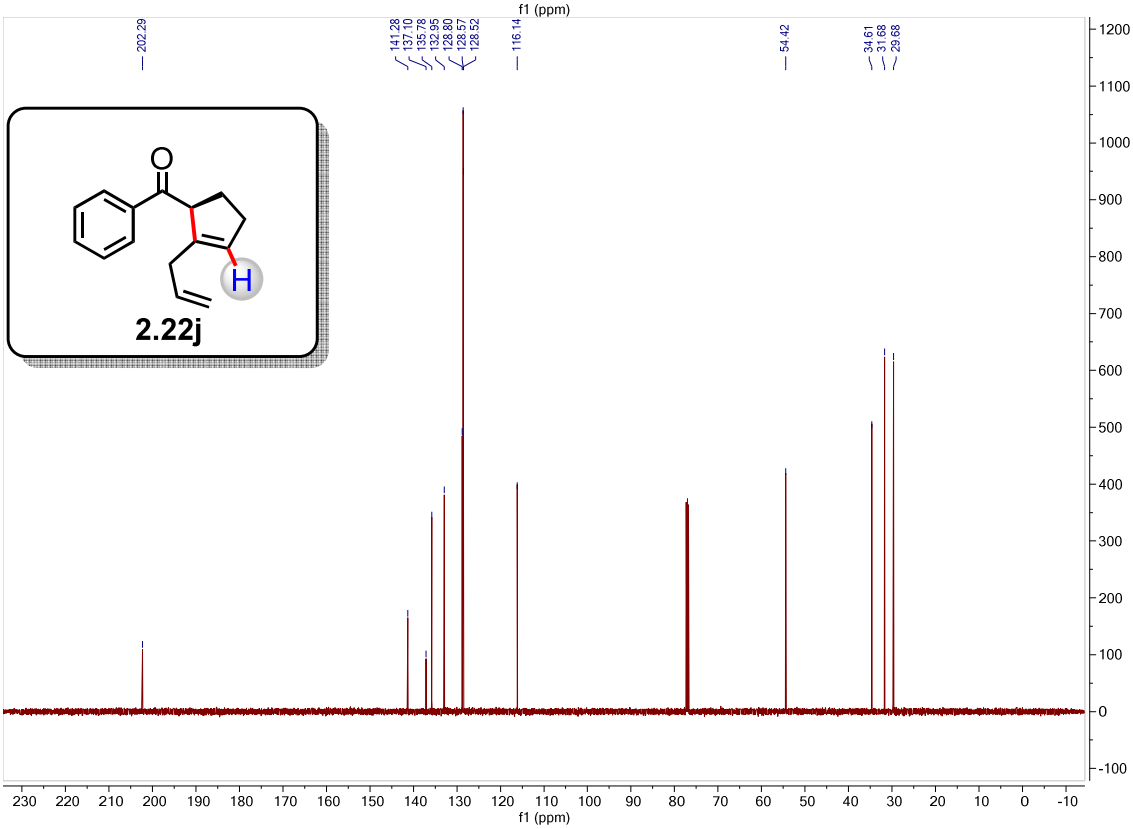

O
Ph
H
2.22h
f1 (ppm)

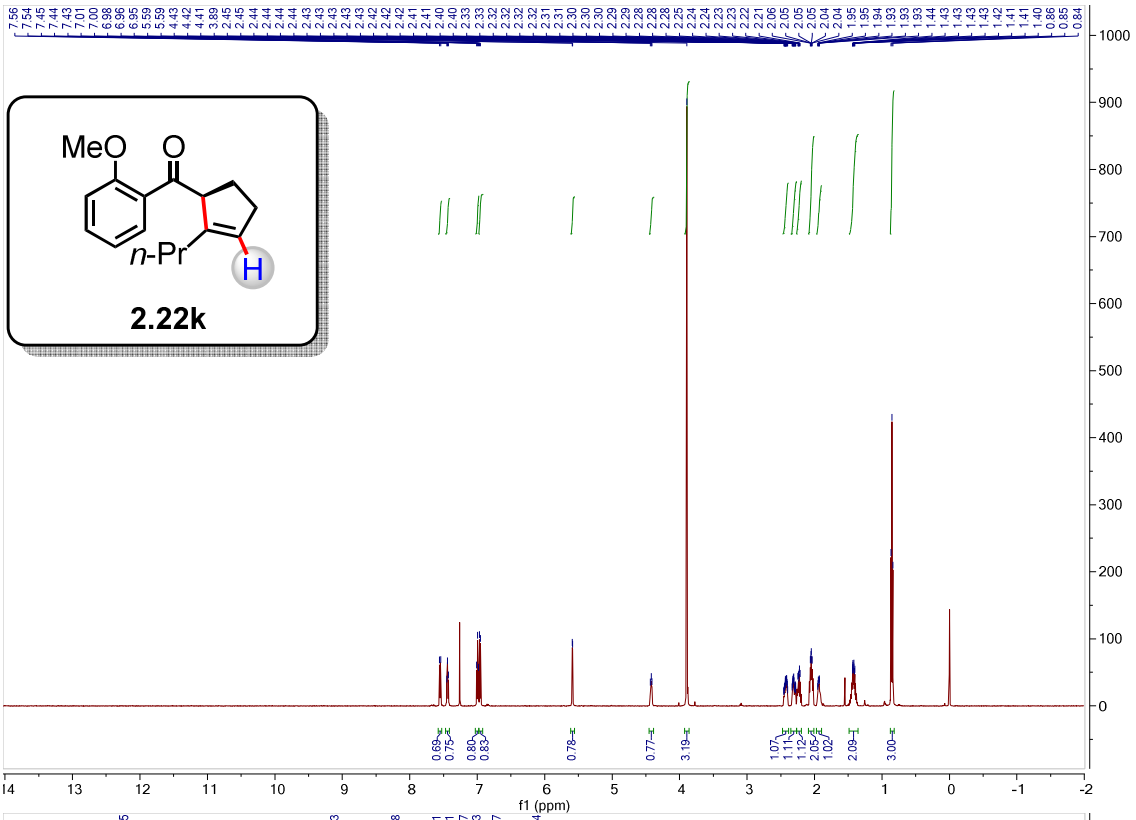

O
Ph
H
2.22h
f1 (ppm)

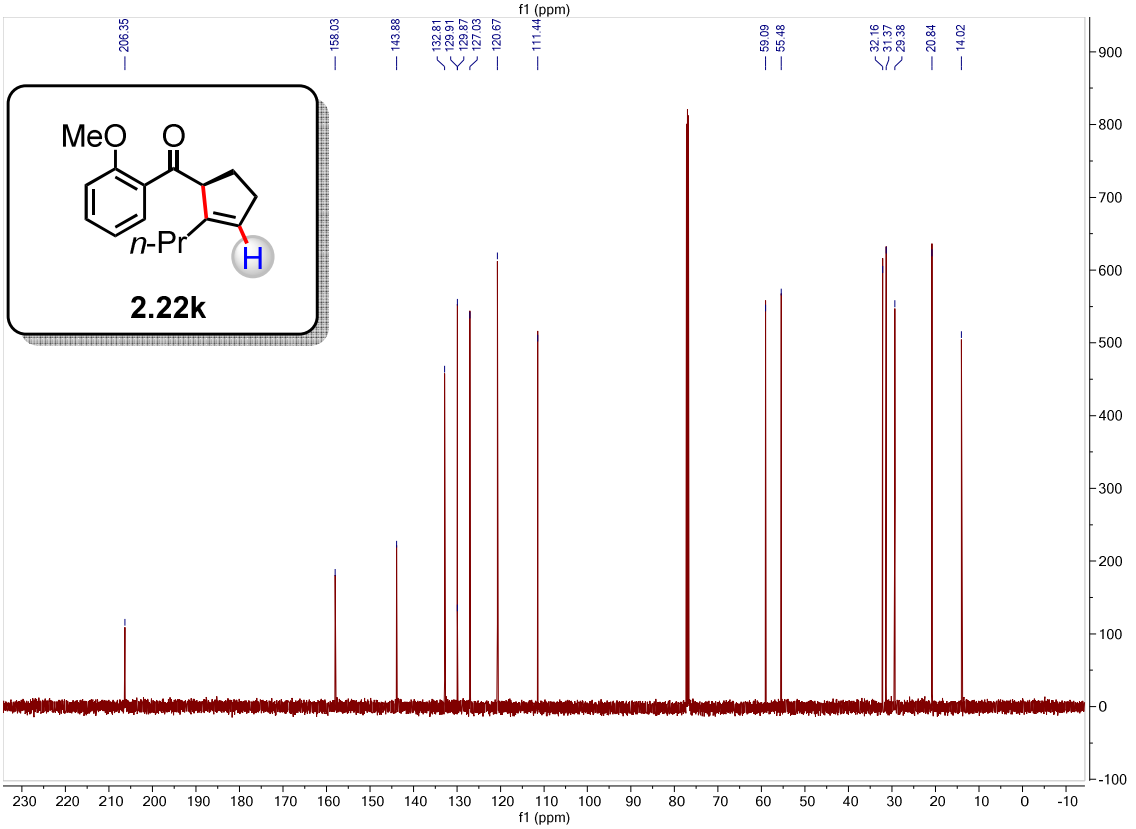

O
H
CO2Me
2.22i
f1 (ppm)


O
H
CO2Me
2.22i
f1 (ppm)


2.22j
f1 (ppm)


2.22j
f1 (ppm)


MeO
O
n-Pr
H
2.22k
f1 (ppm)


MeO
O
n-Pr
H
2.22k
206.35
158.03
143.88
132.81
129.91
129.87
127.03
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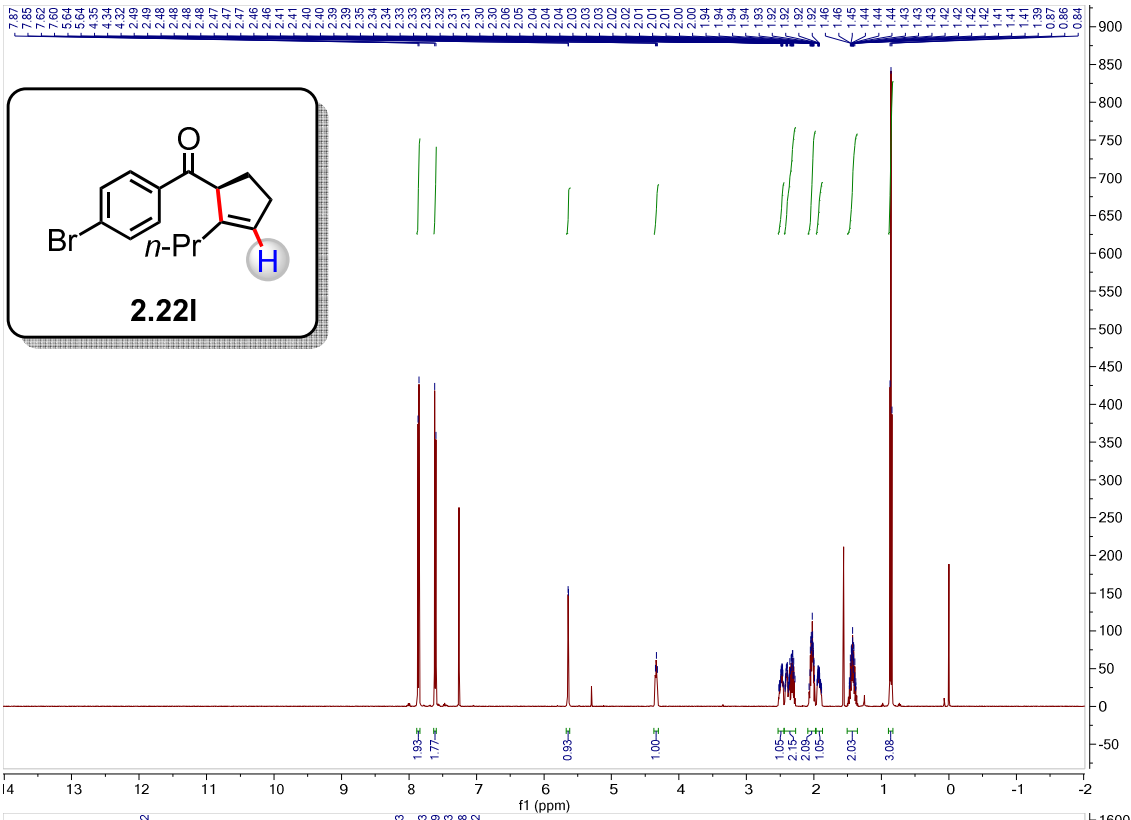
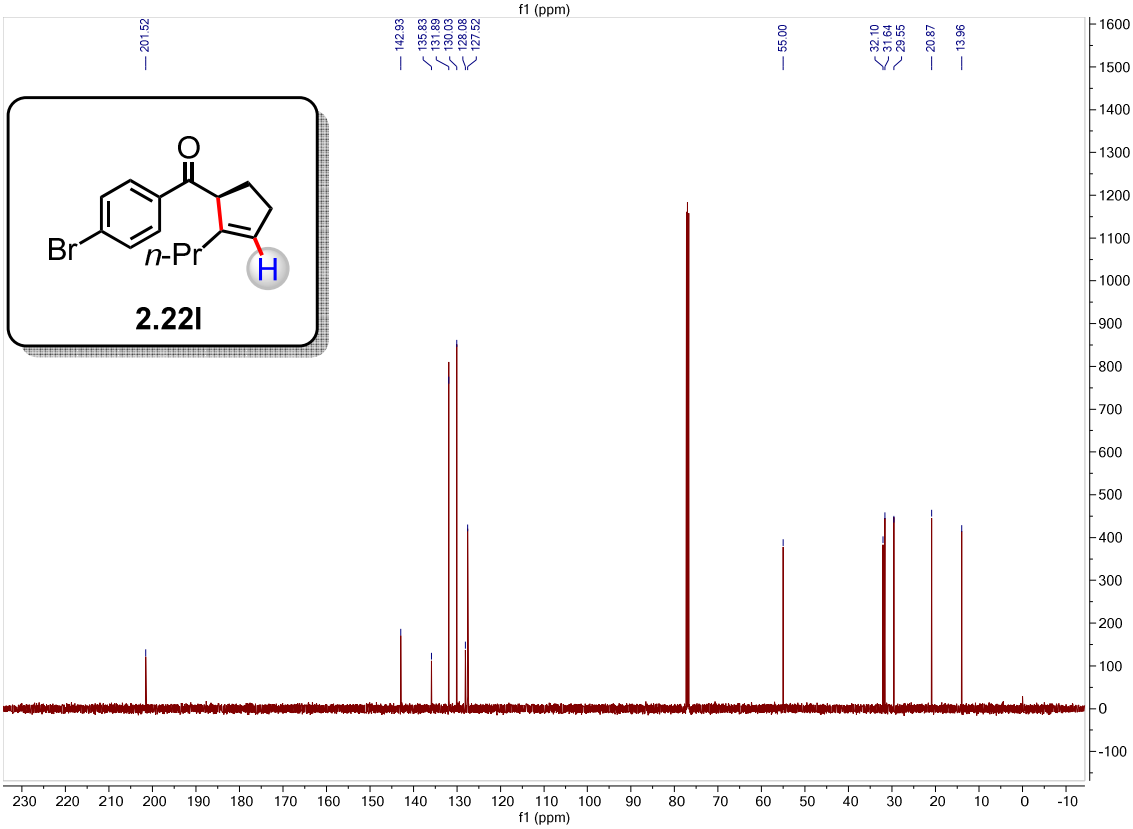
111.44
59.09
55.48
32.16
31.37
29.38
20.84
14.02
f1 (ppm)


O
Br
n-Pr
H
2.22l
f1 (ppm)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131.89
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128.08
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55.00
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31.64
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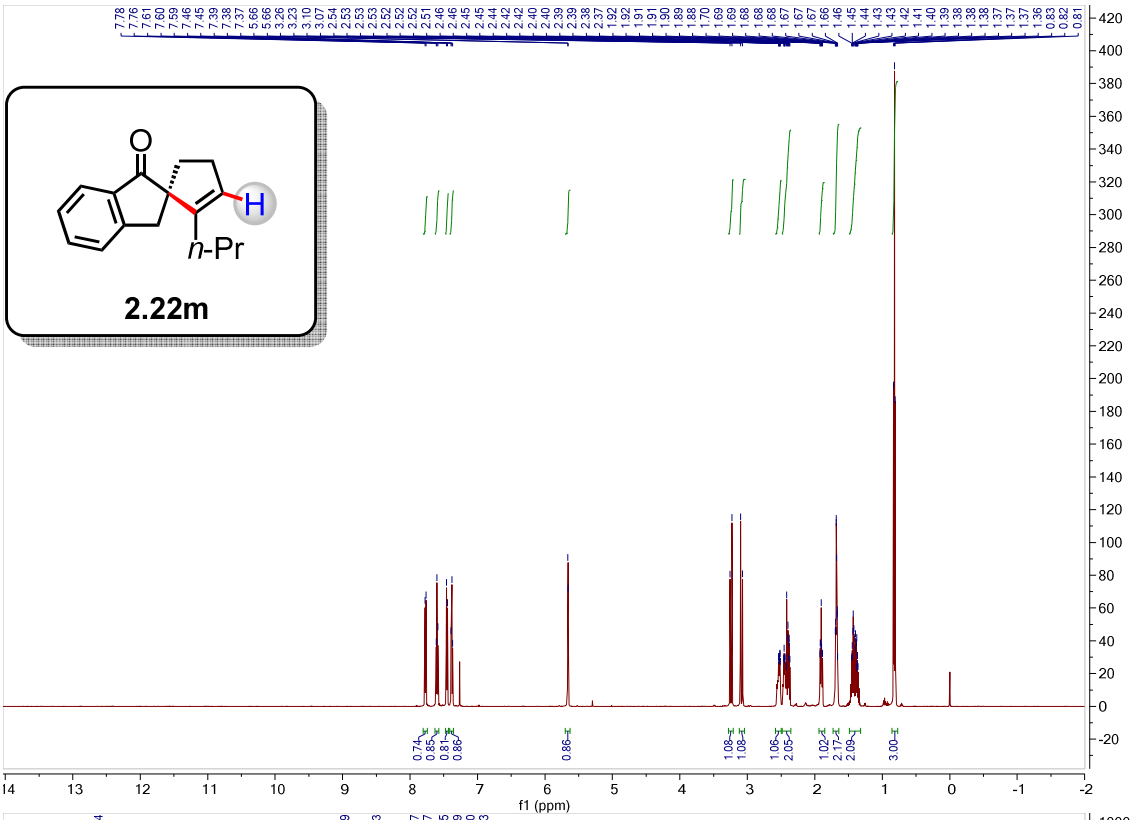
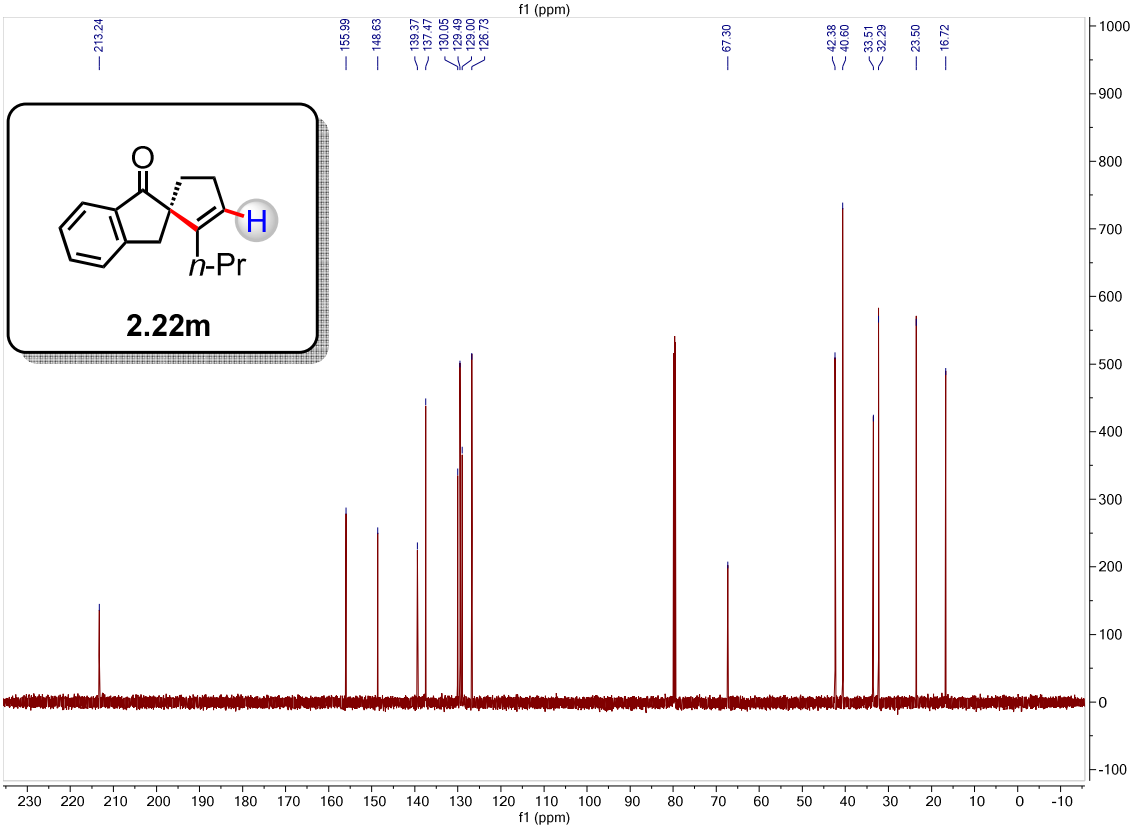
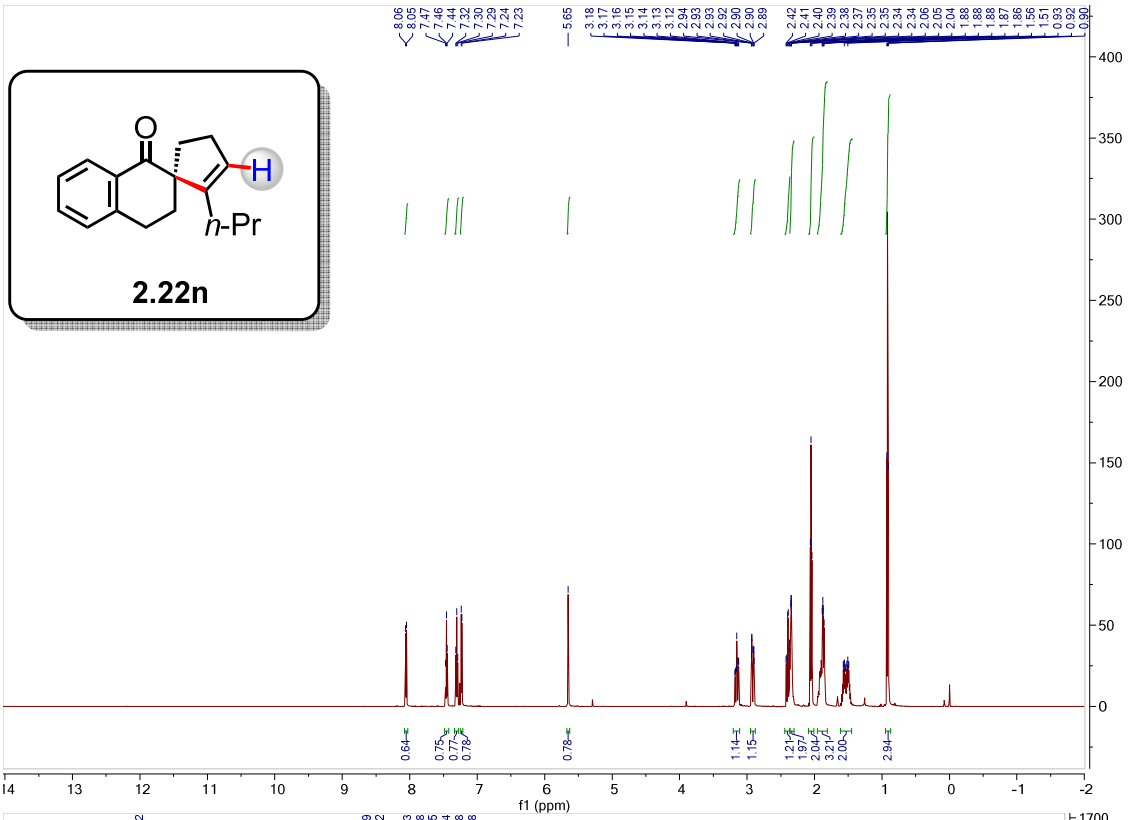
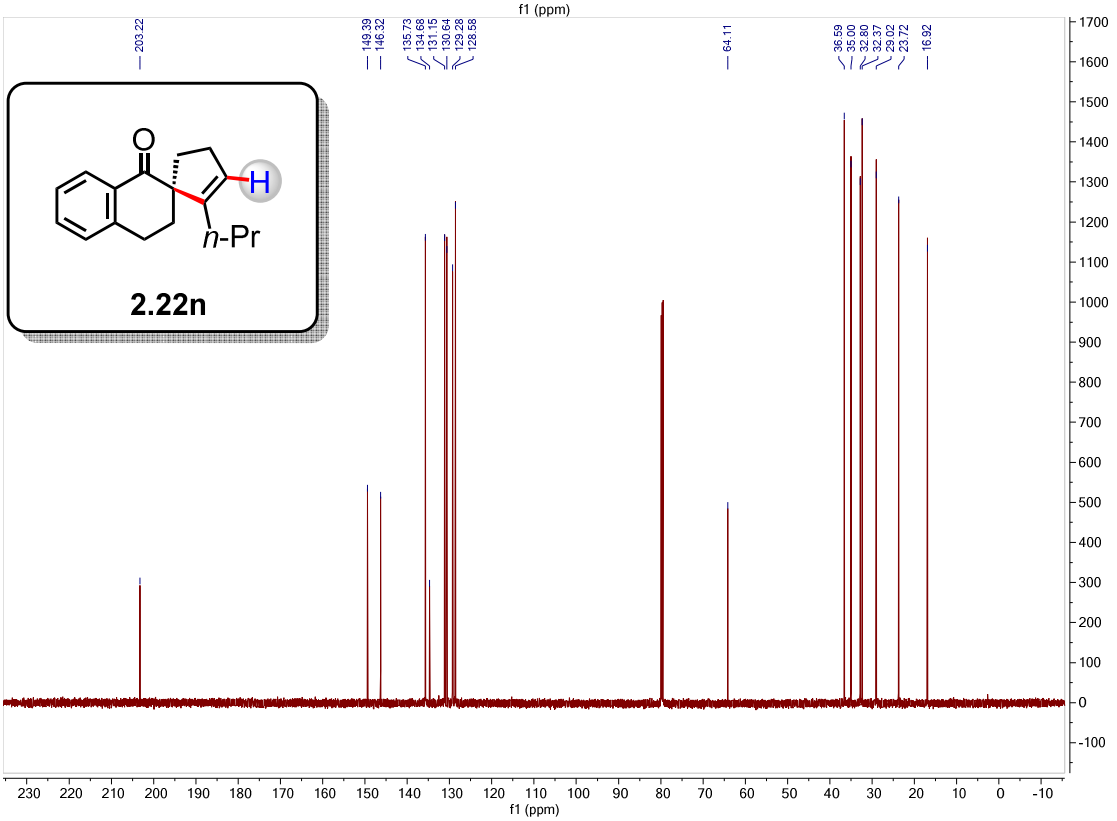
20.87
13.96
O
Br
n-Pr
H
2.22l
f1 (ppm)


H
n-Pr
2.22m
f1 (ppm)


H
n-Pr
2.22m
f1 (ppm)


O
H
n-Pr
2.22n
f1 (ppm)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H
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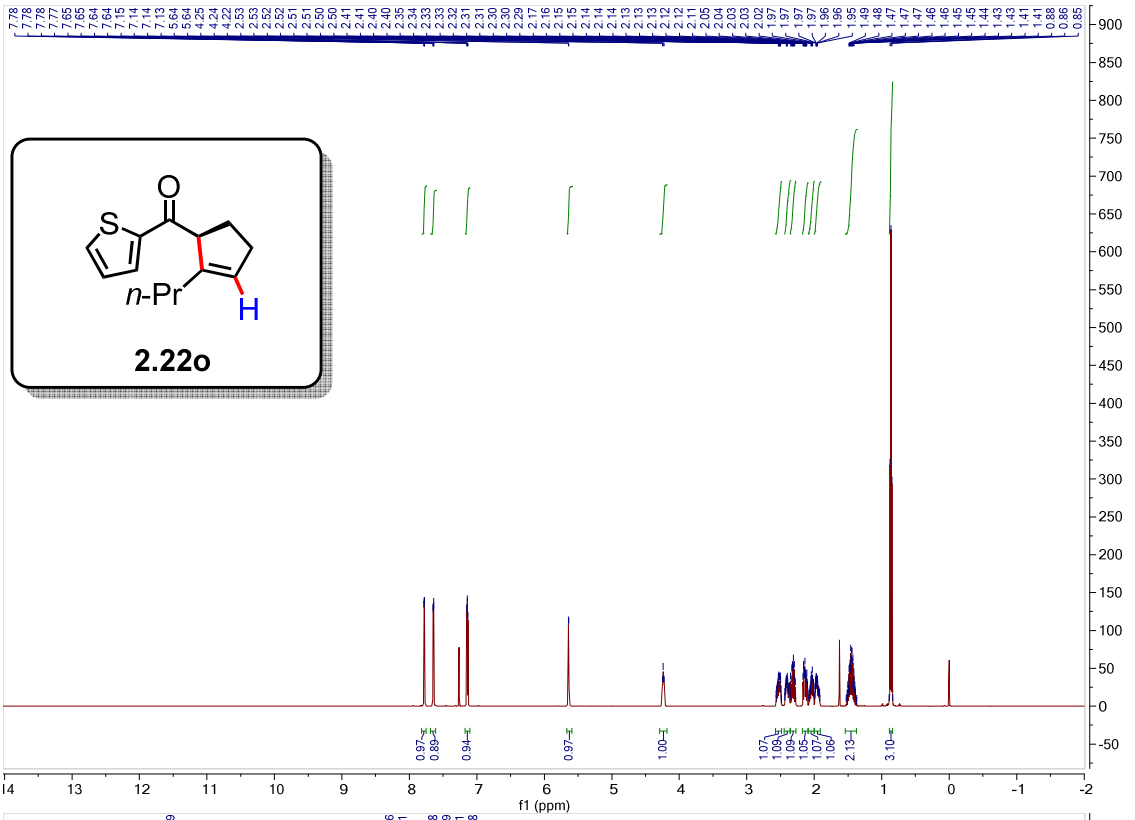
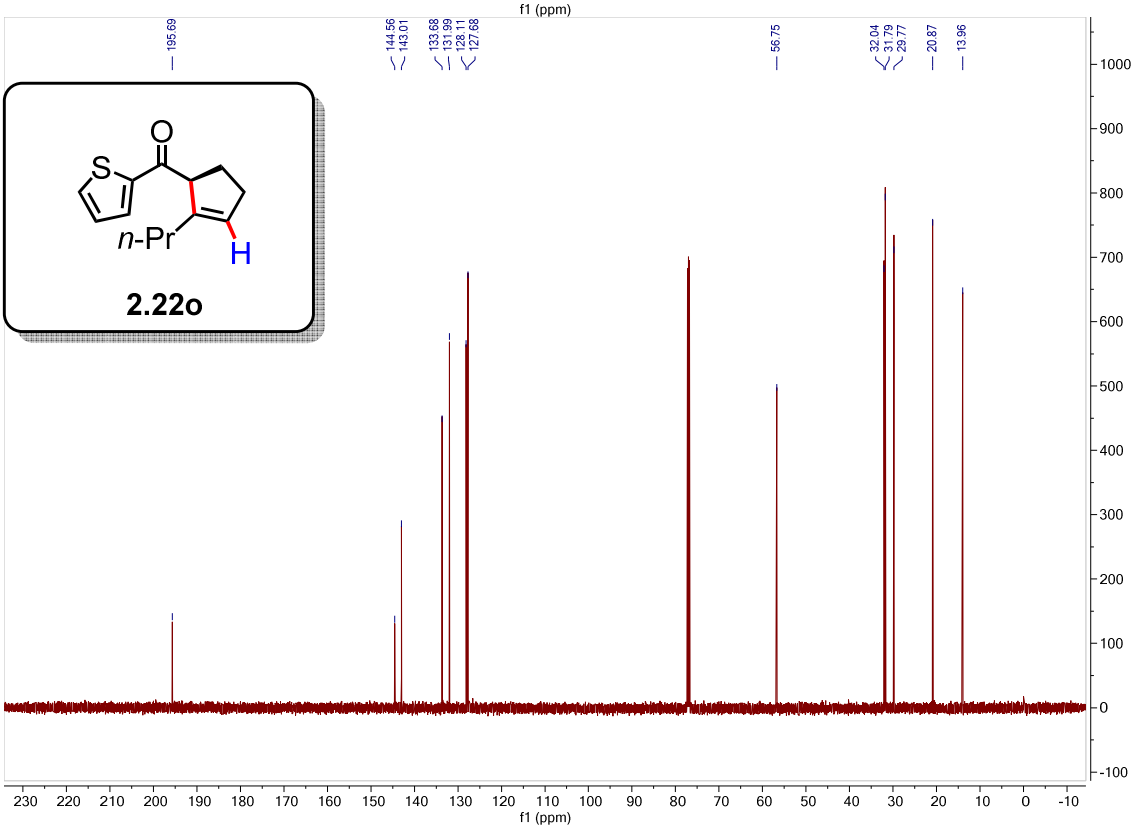
2.22n
f1 (ppm)


O
S
n-Pr
H
2.22o
f1 (ppm)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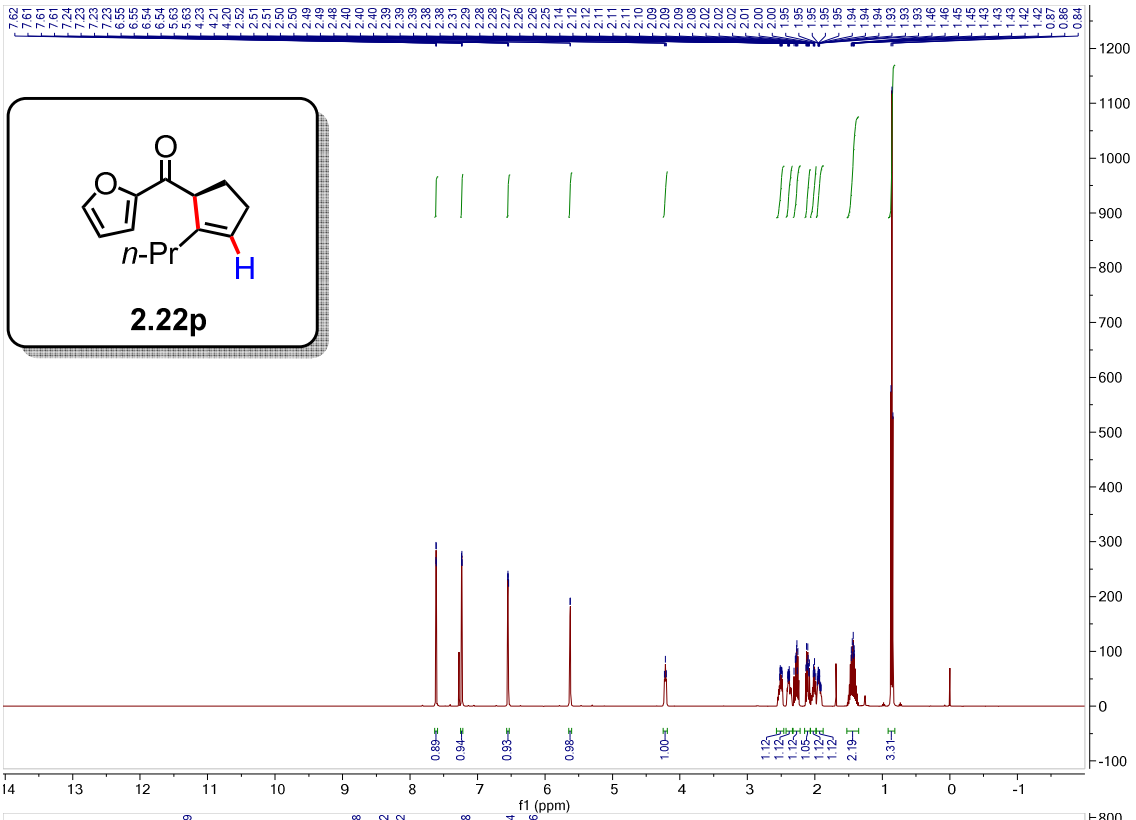
32.04
31.79
29.77
20.87
13.96
O
S
n-Pr
H
2.22o
f1 (ppm)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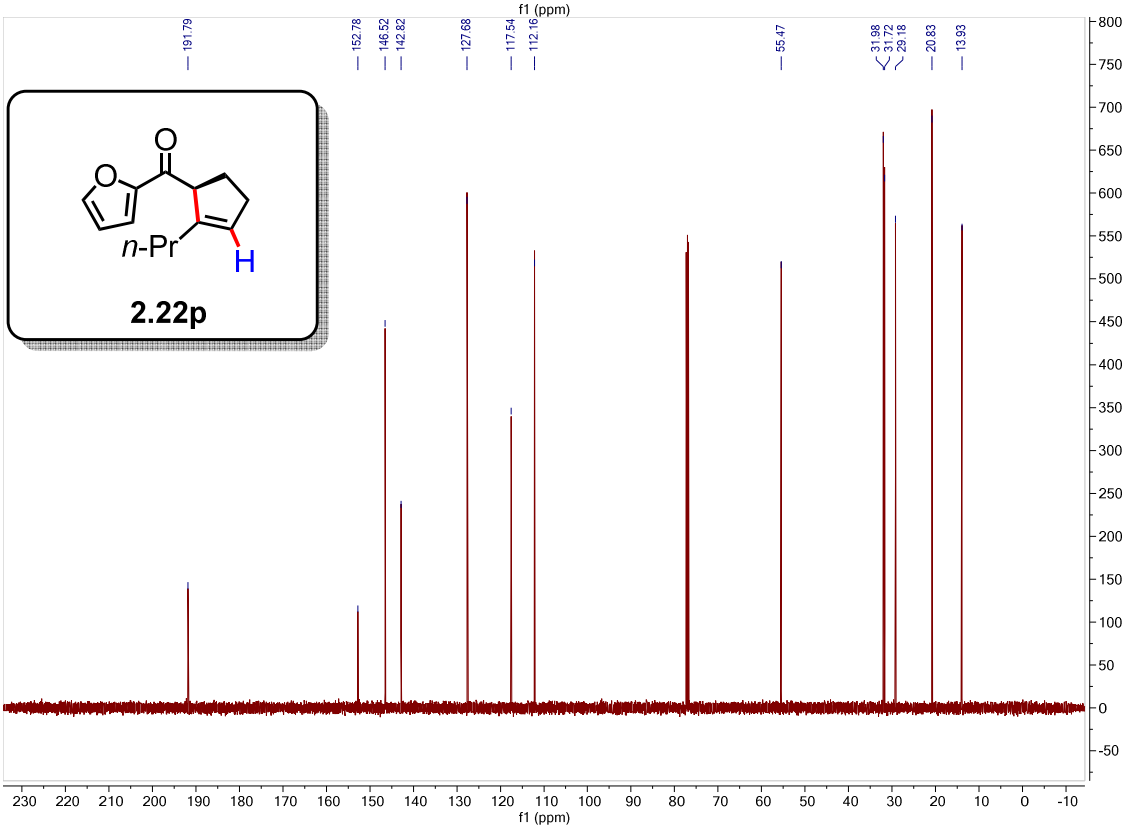
H
2.22p
f1 (ppm)


n-Pr
H
2.22p
191.79
152.78
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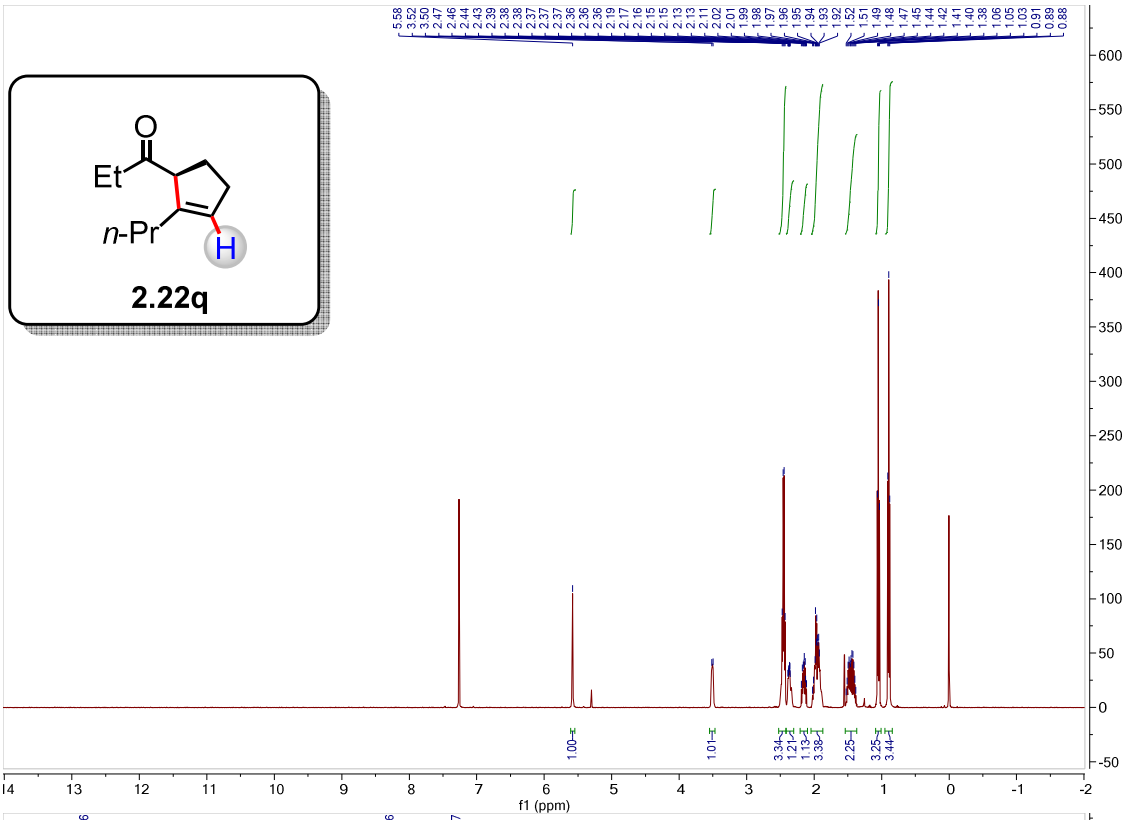
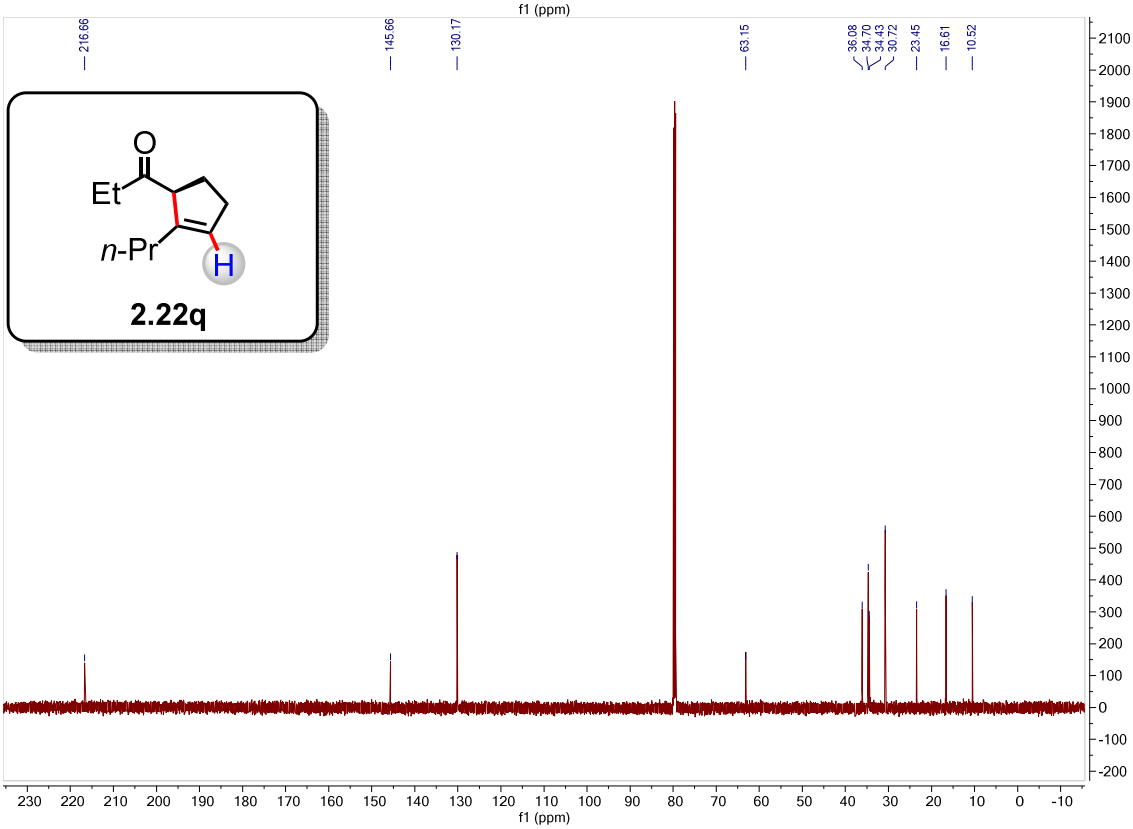
117.54
112.16
55.47
31.98
31.72
29.18
20.83
13.93
f1 (ppm)


Et
n-Pr
H
2.22q
f1 (ppm)


Et
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H
2.22q
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36.08
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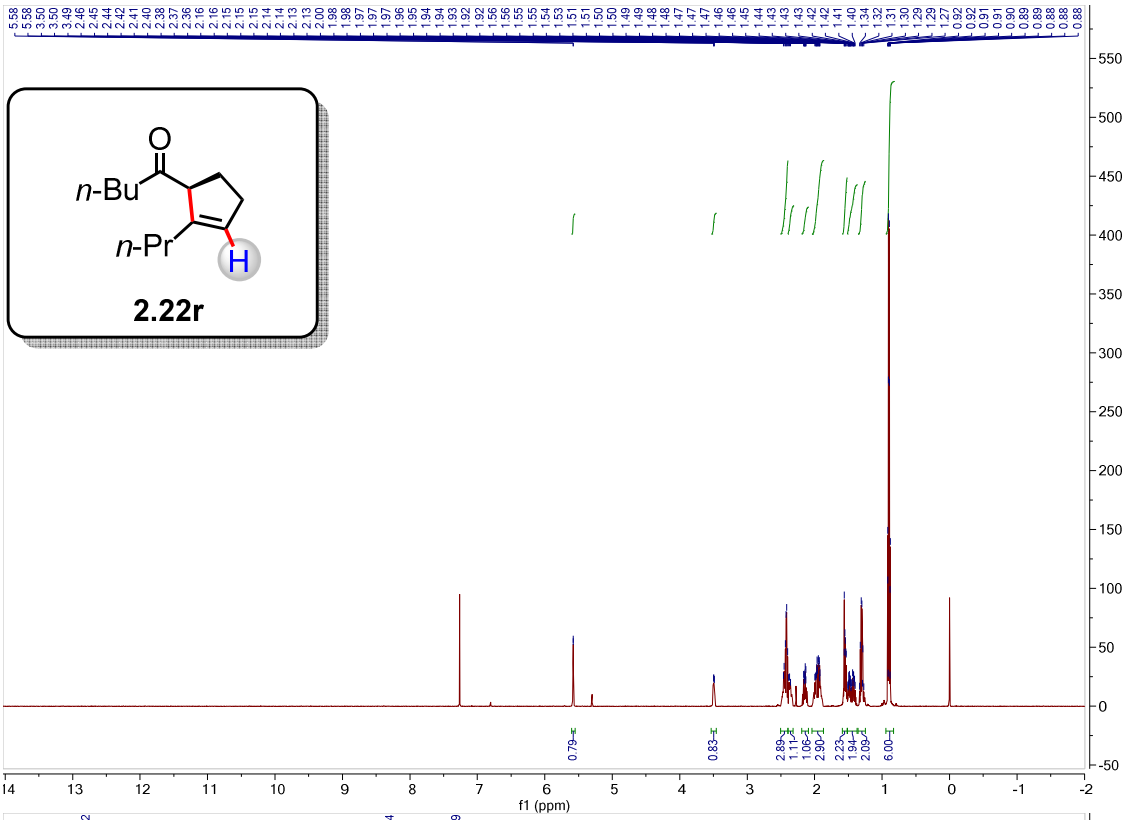
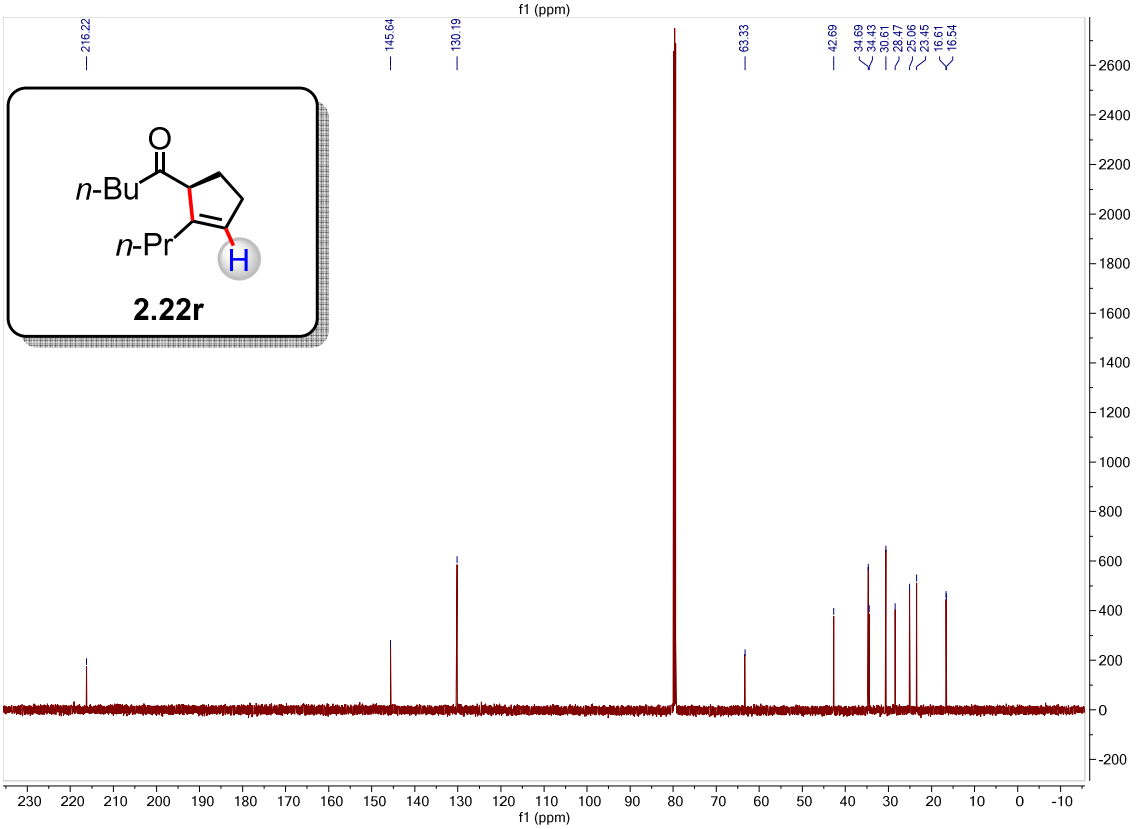
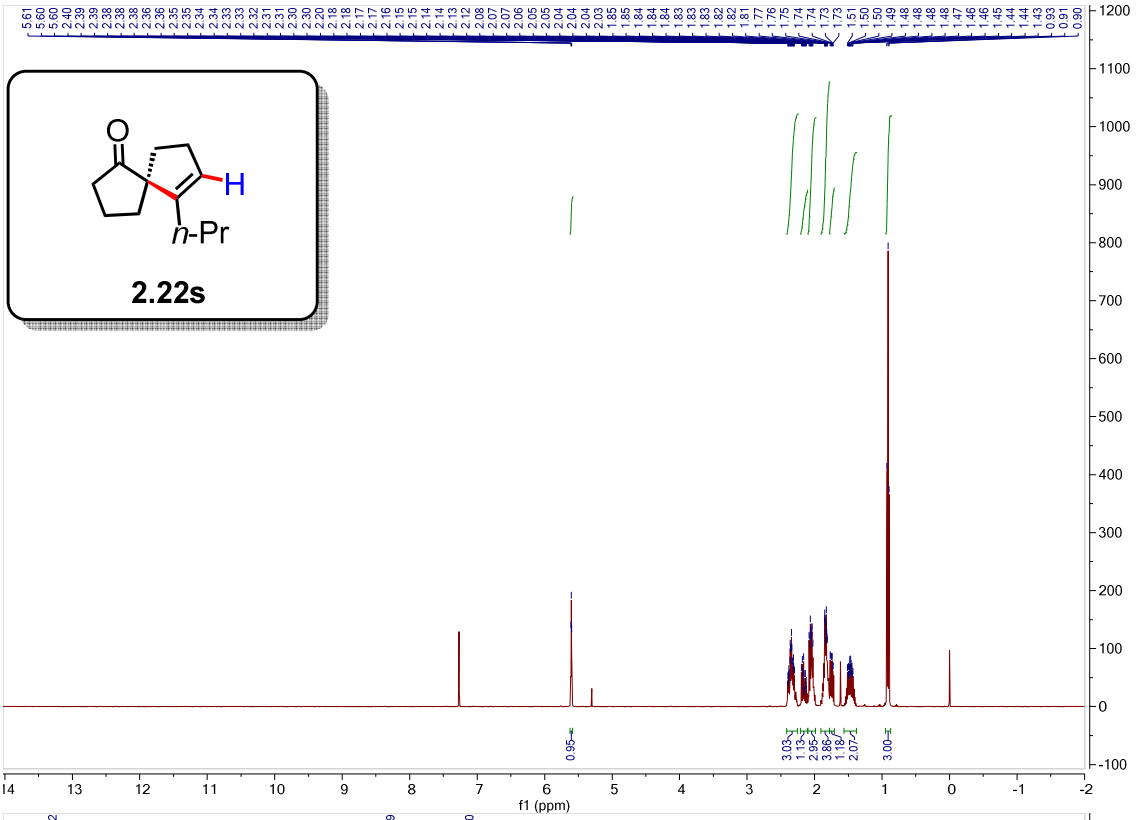
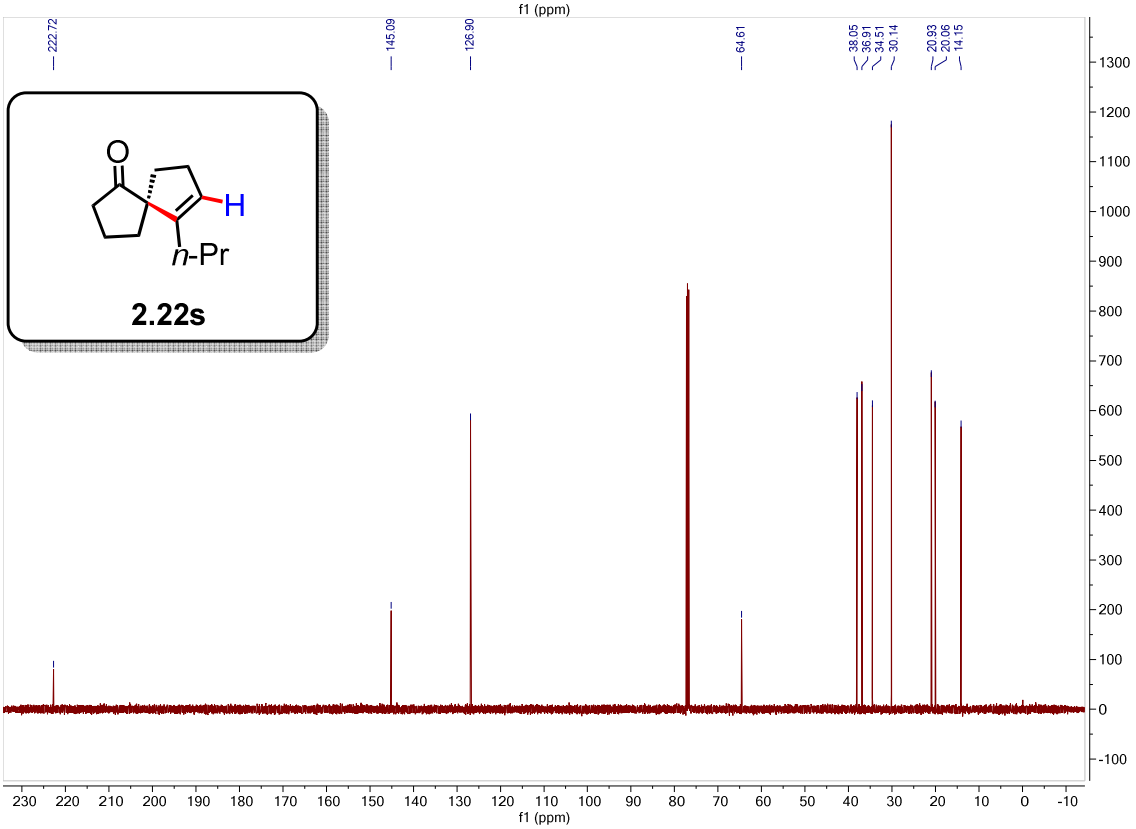
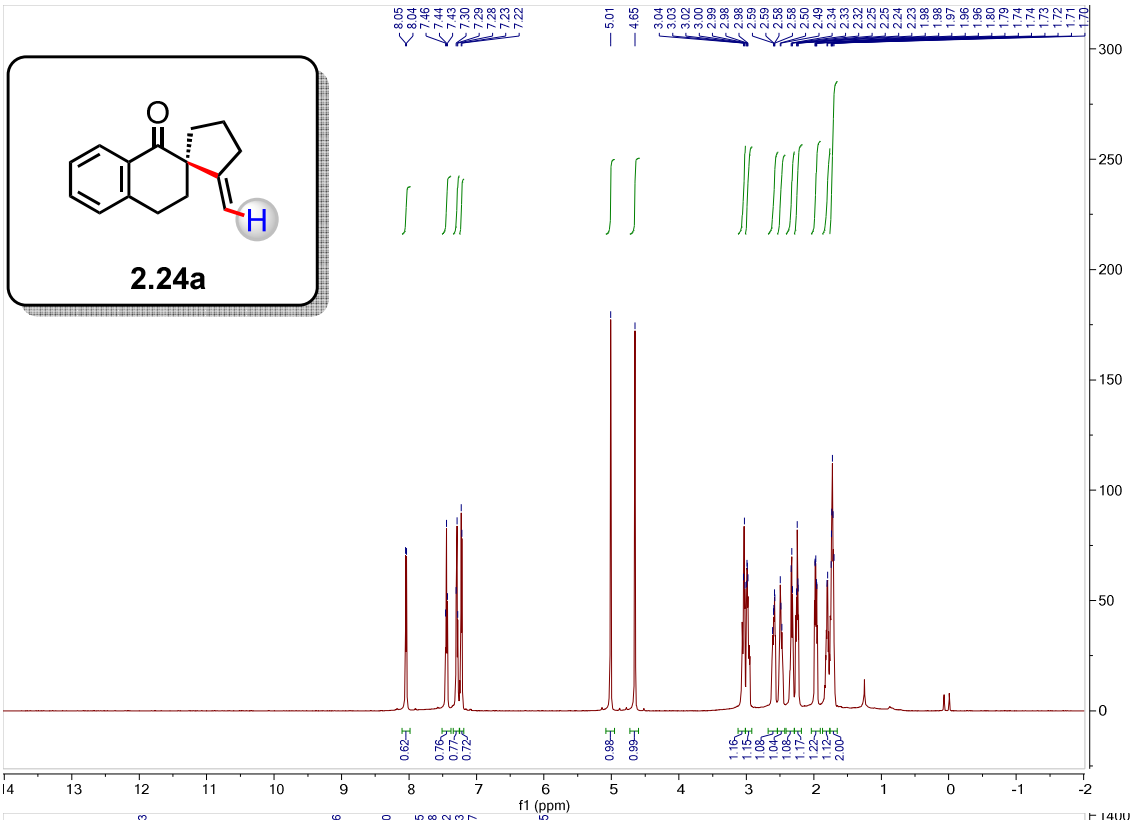
23.45
16.61
10.52
f1 (ppm)

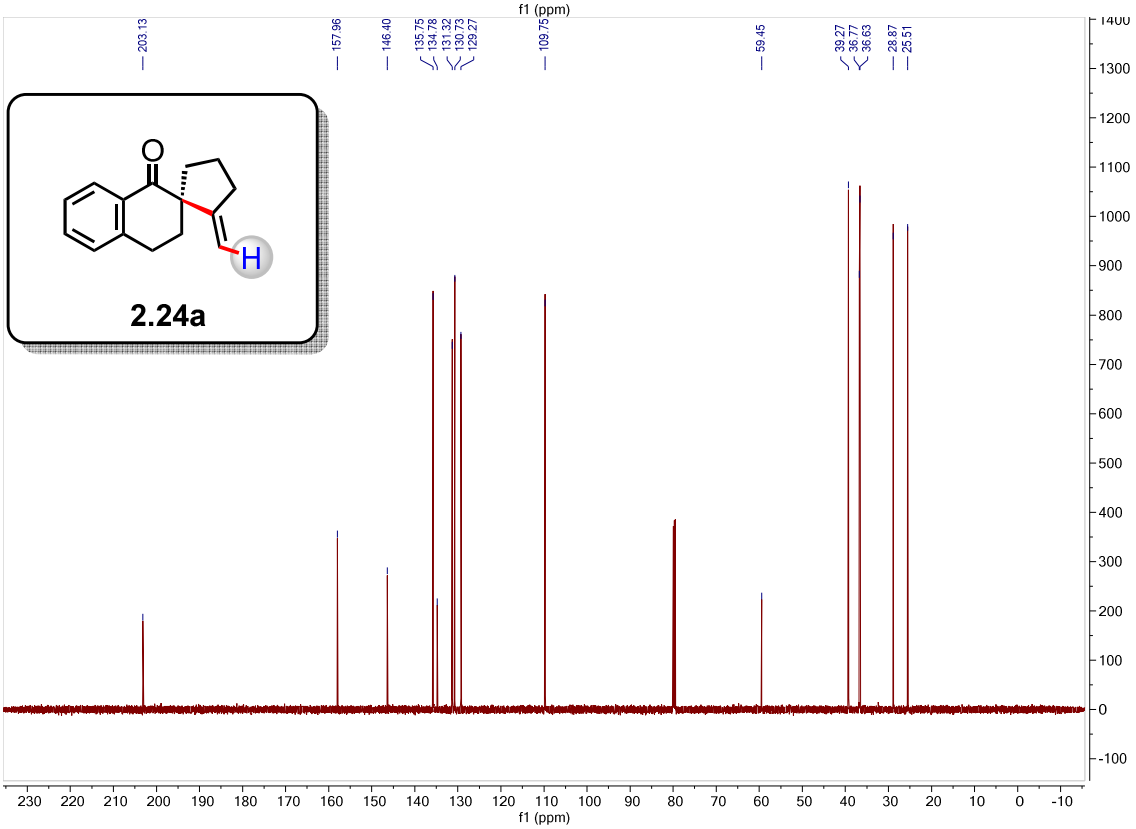

n-Bu
n-Pr
H
2.22r
f1 (ppm)

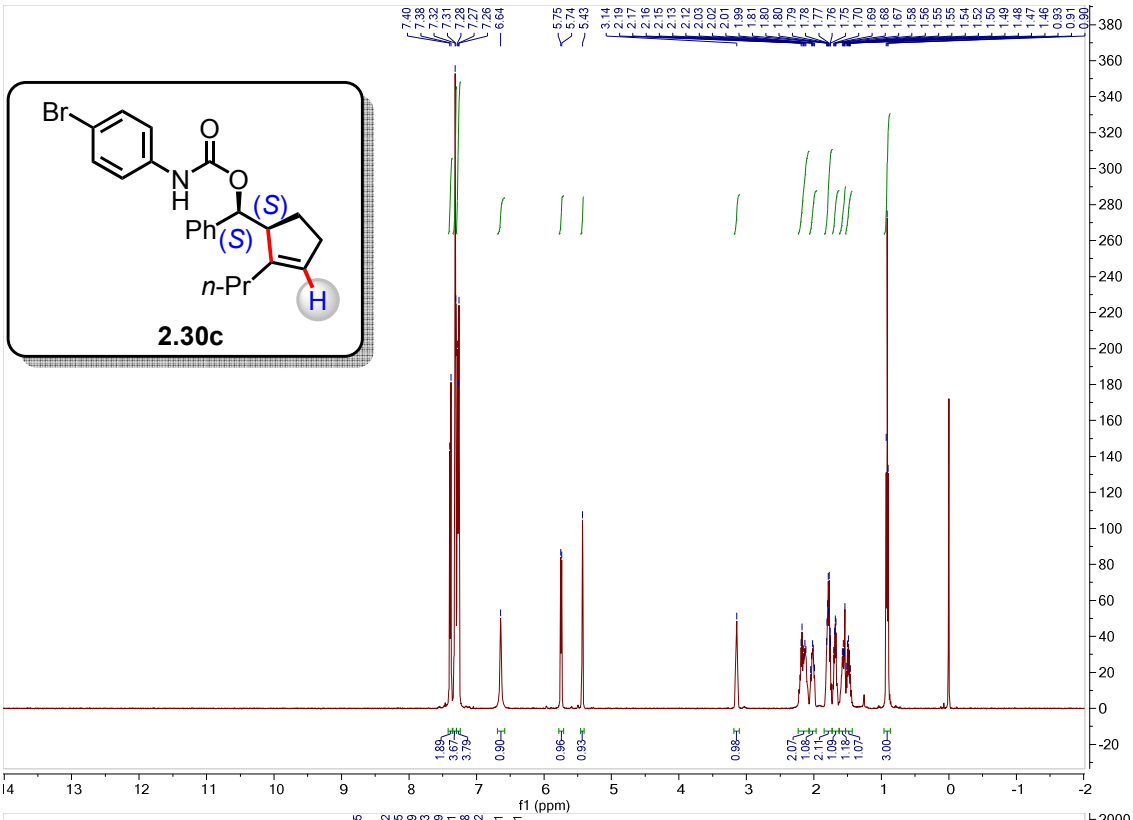

216.22
145.64
130.19
63.33
42.69
34.69
34.43
30.61
28.47
25.06
23.45
16.61
16.54
n-Bu
n-Pr
H
2.22r
f1 (ppm)

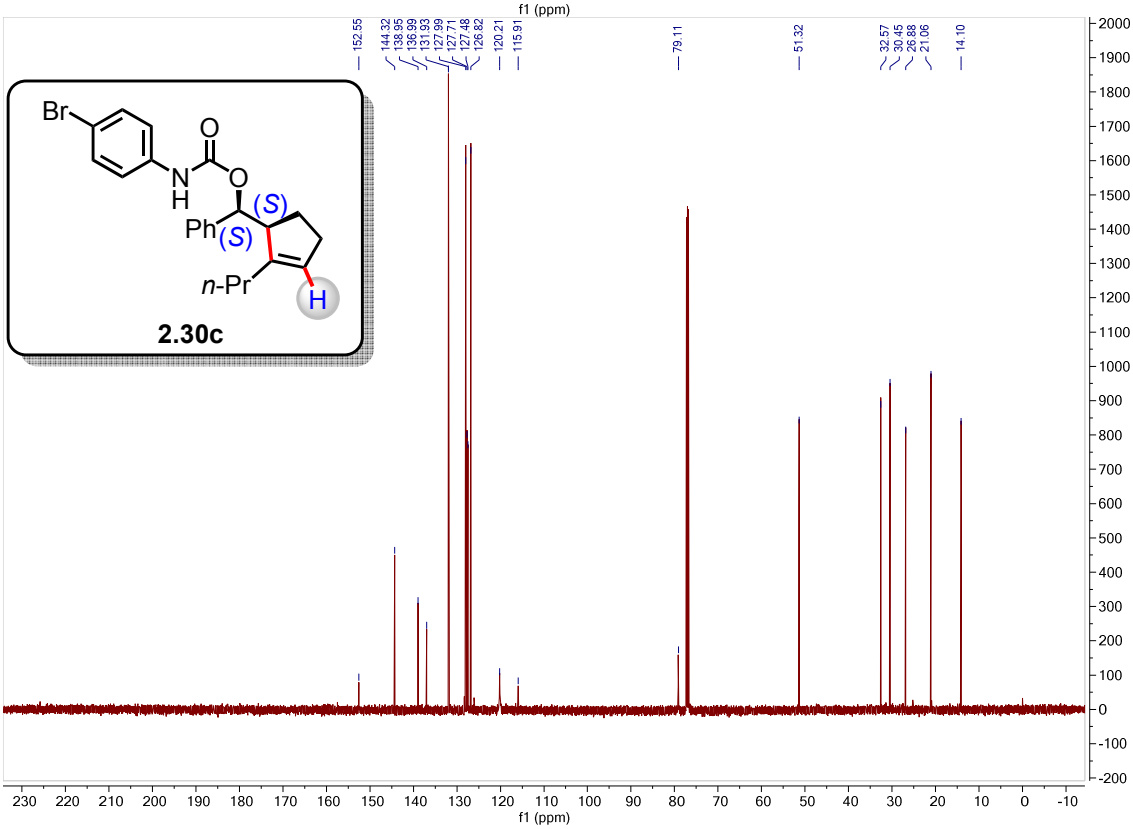

O
H
n-Pr
2.22s
f1 (ppm)

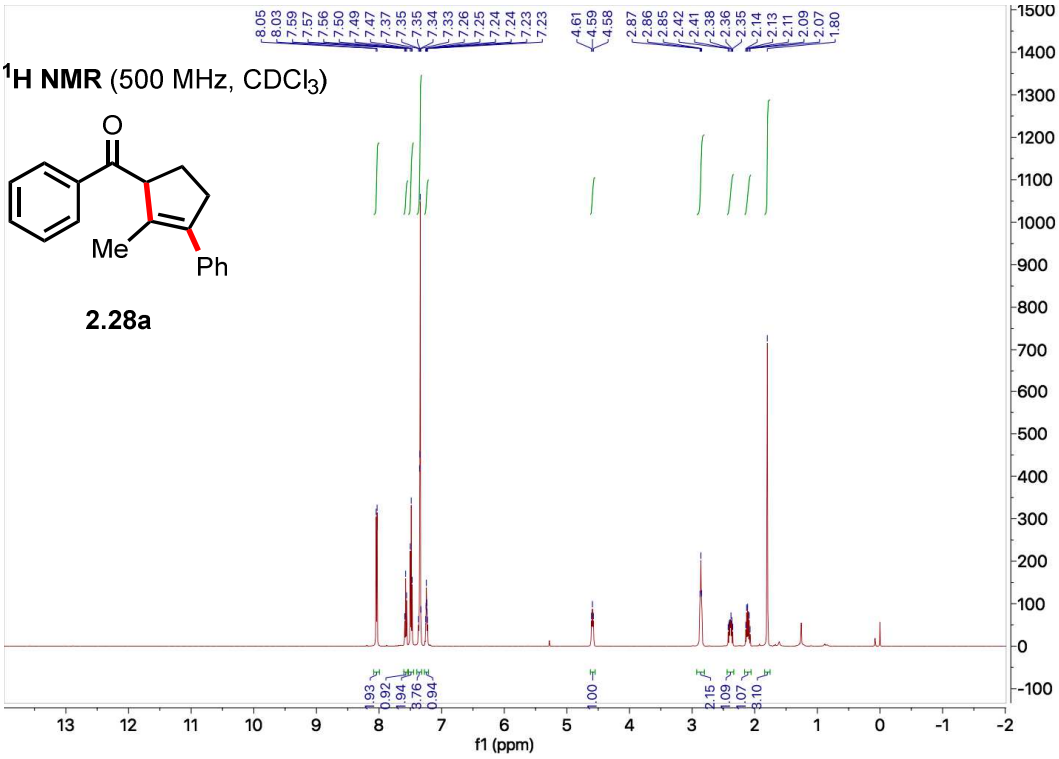

222.72
145.09
126.90
64.61
38.05
36.91
34.51
30.14
20.93
20.06
14.15
O
H
n-Pr
2.22s
f1 (ppm)

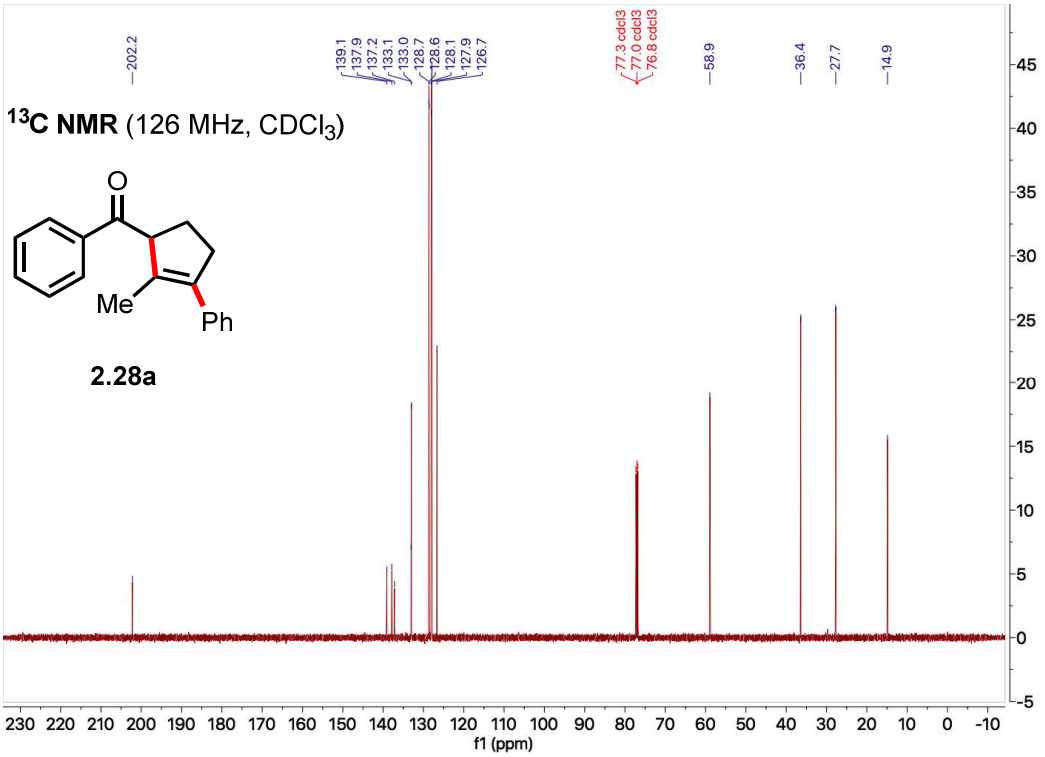

2.24a
f1 (ppm)

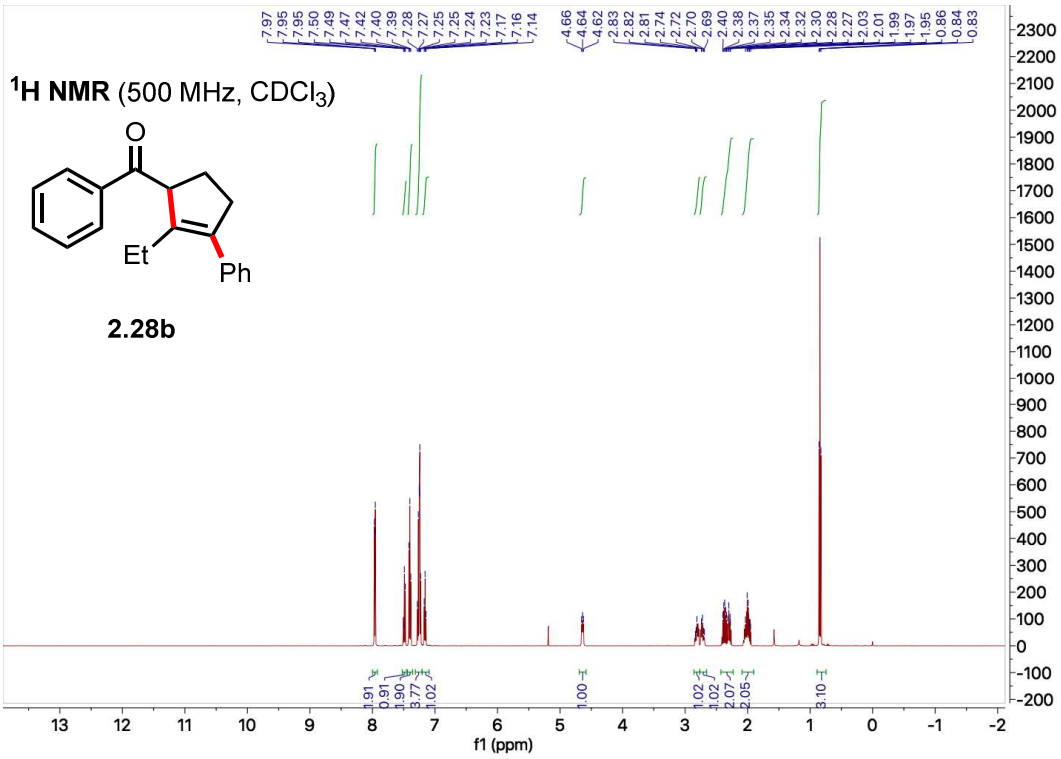

2.24a
f1 (ppm)

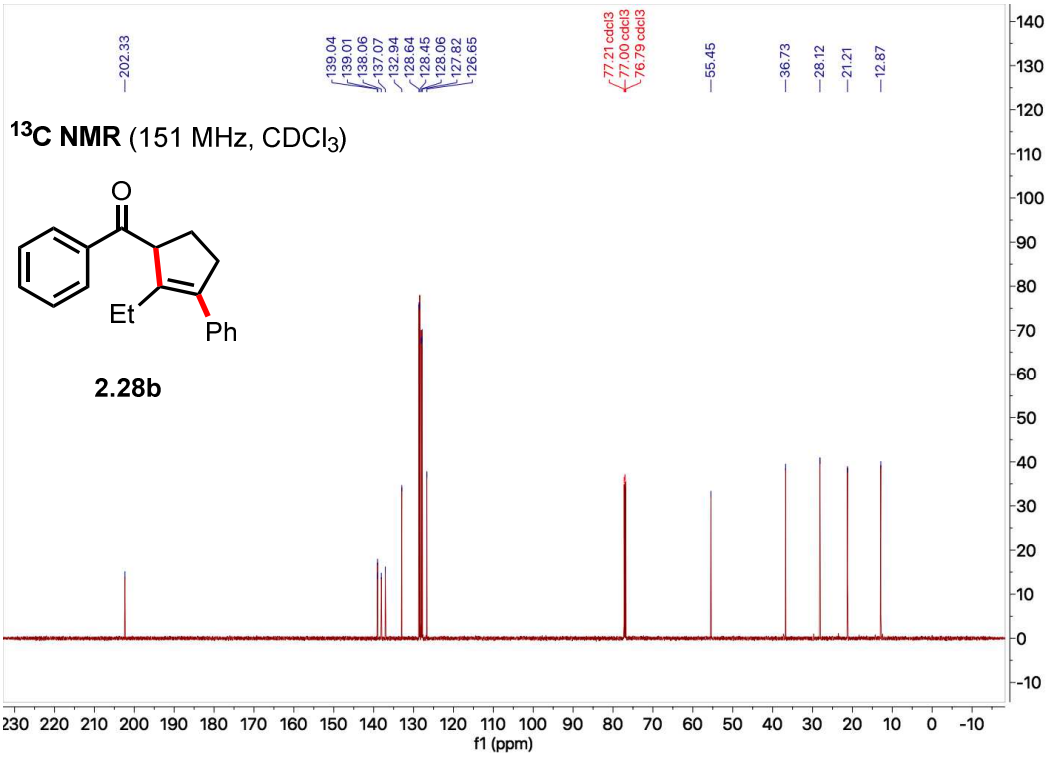

Br
O
N
H
O
(S)
Ph
(S)
n-Pr
H
2.30c
f1 (ppm)

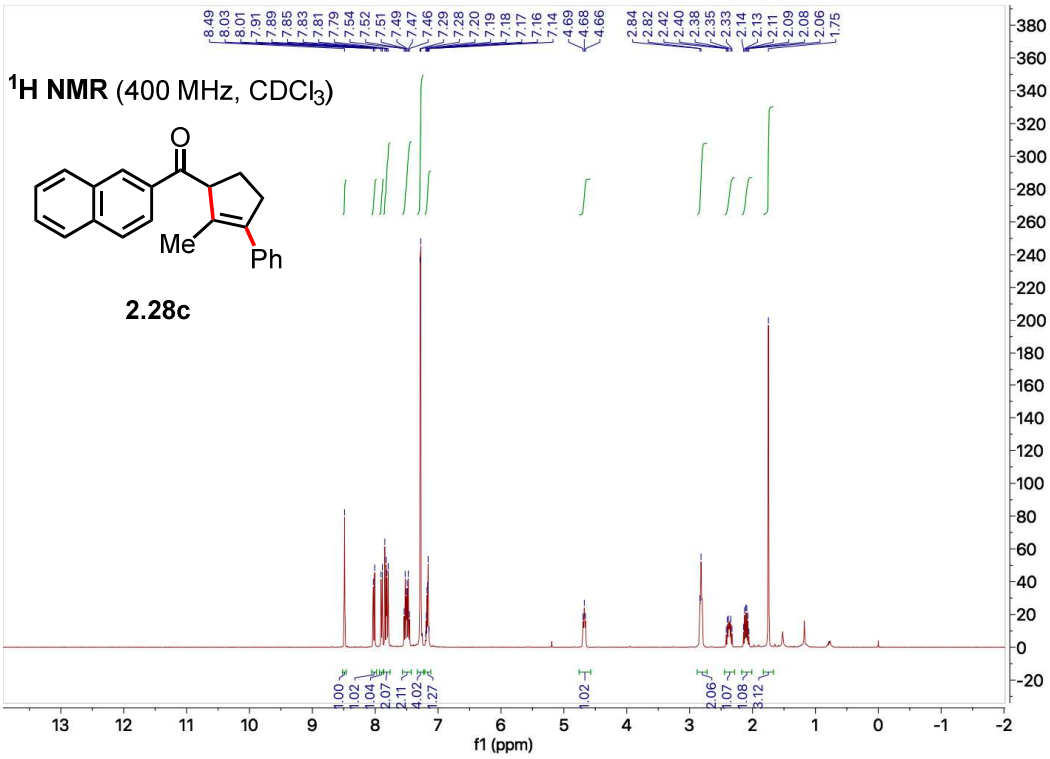

Br
O
N
H
O
(S)
Ph
(S)
n-Pr
H
2.30c
f1 (ppm)

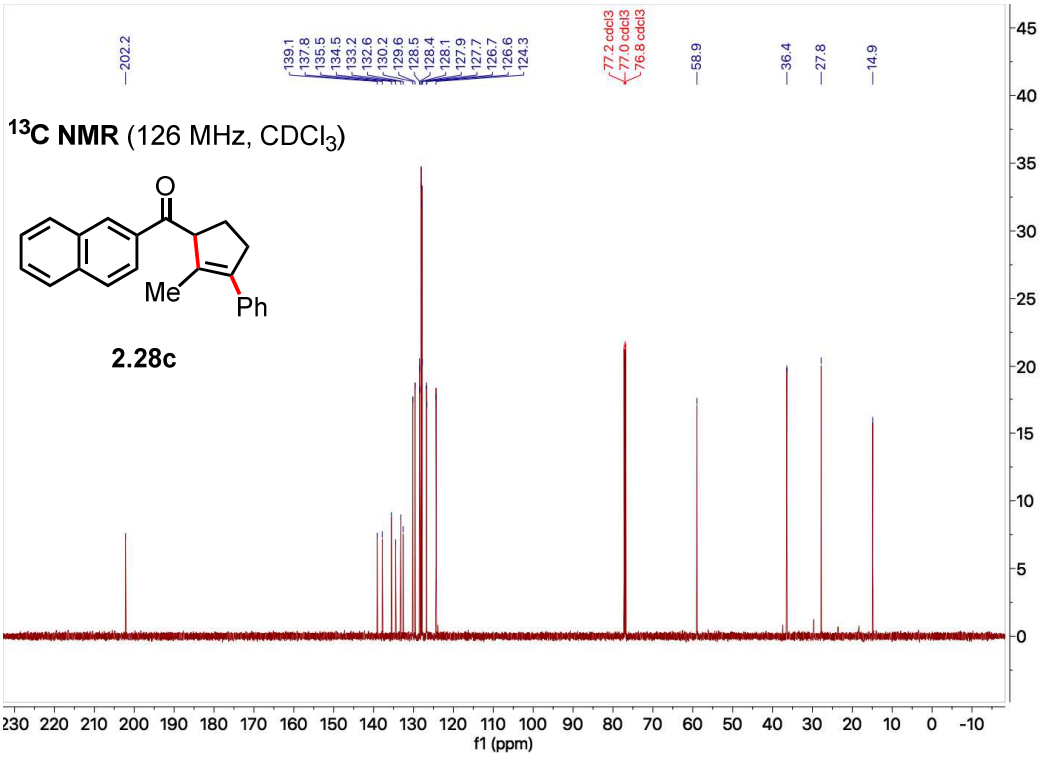

1H NMR (500 MHz, CDCl3)
O
Me
Ph
2.28a
f1 (ppm)

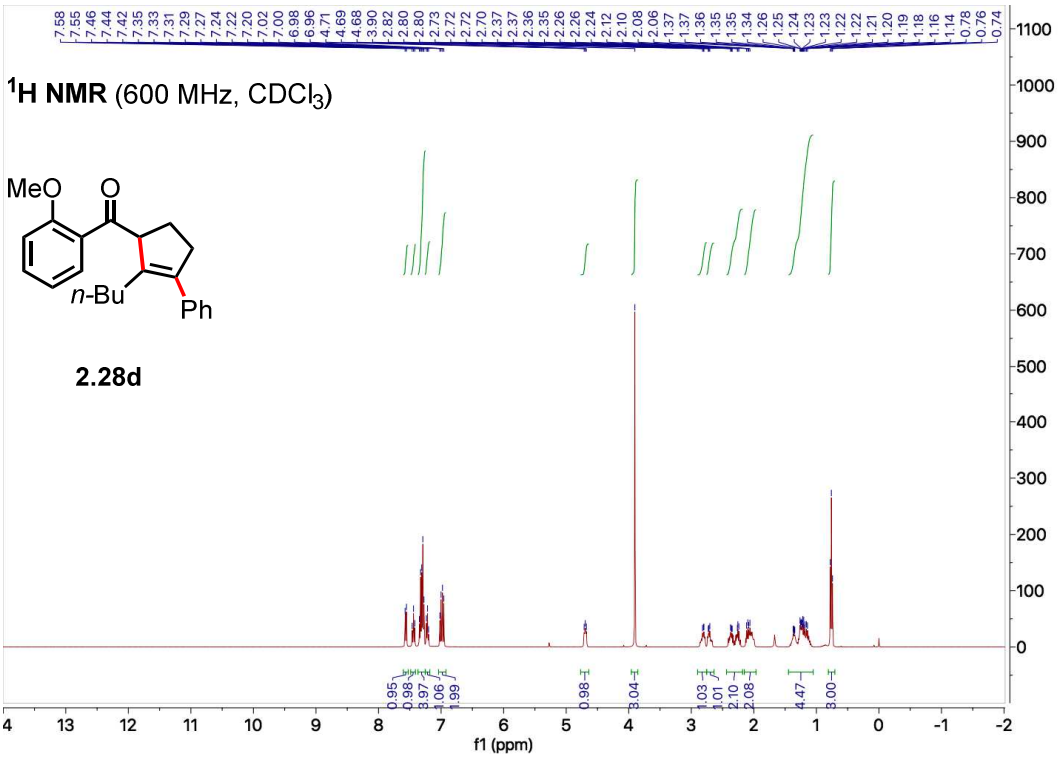

13C NMR (126 MHz, CDCl3)
O
Me
Ph
2.28a
f1 (ppm)

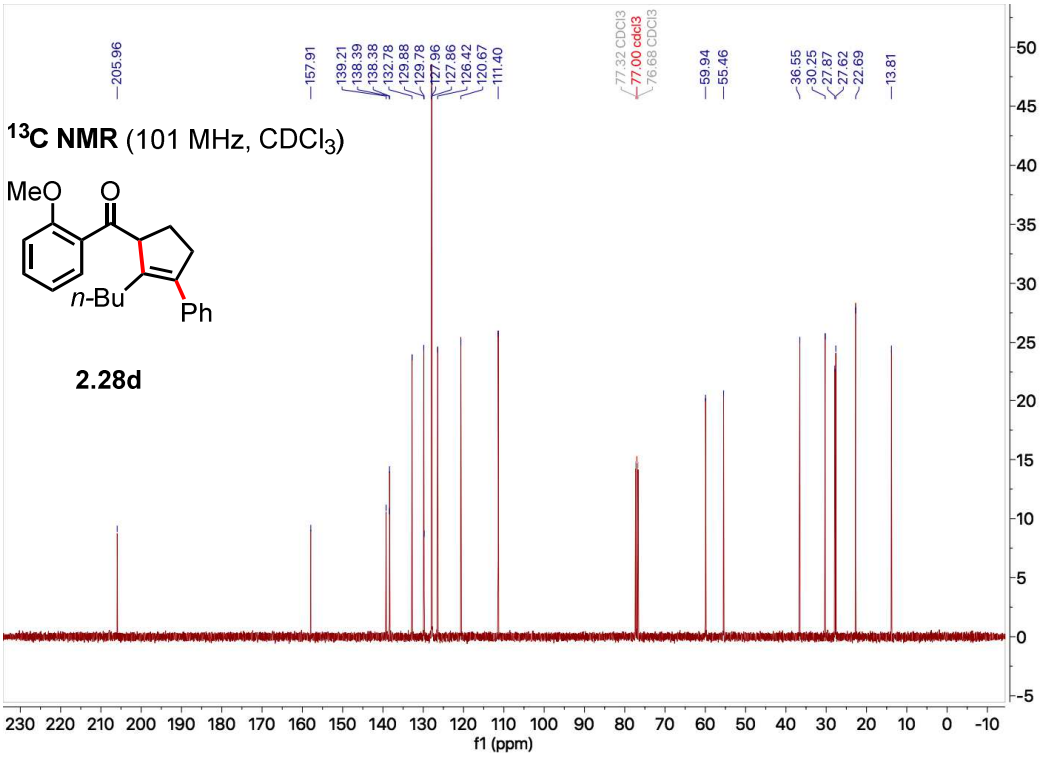

1H NMR (500 MHz, CDCl3)
O
Et
Ph
2.28b
f1 (ppm)

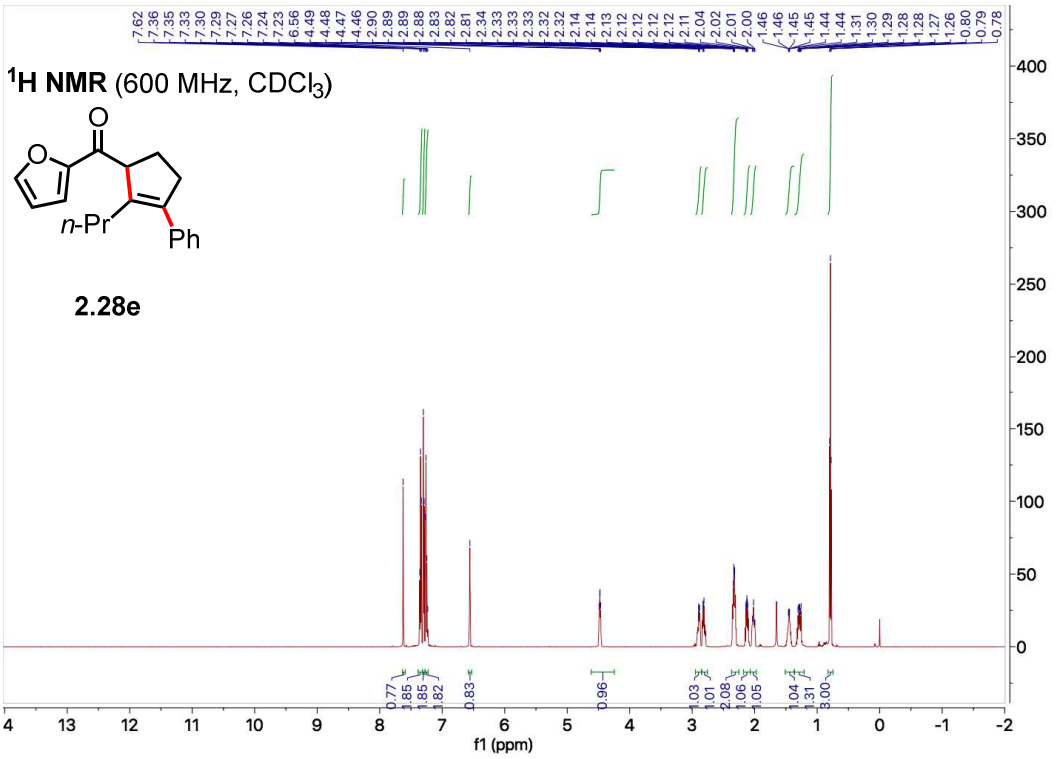

13C NMR (151 MHz, CDCl3)
O
Et
Ph
2.28b
f1 (ppm)

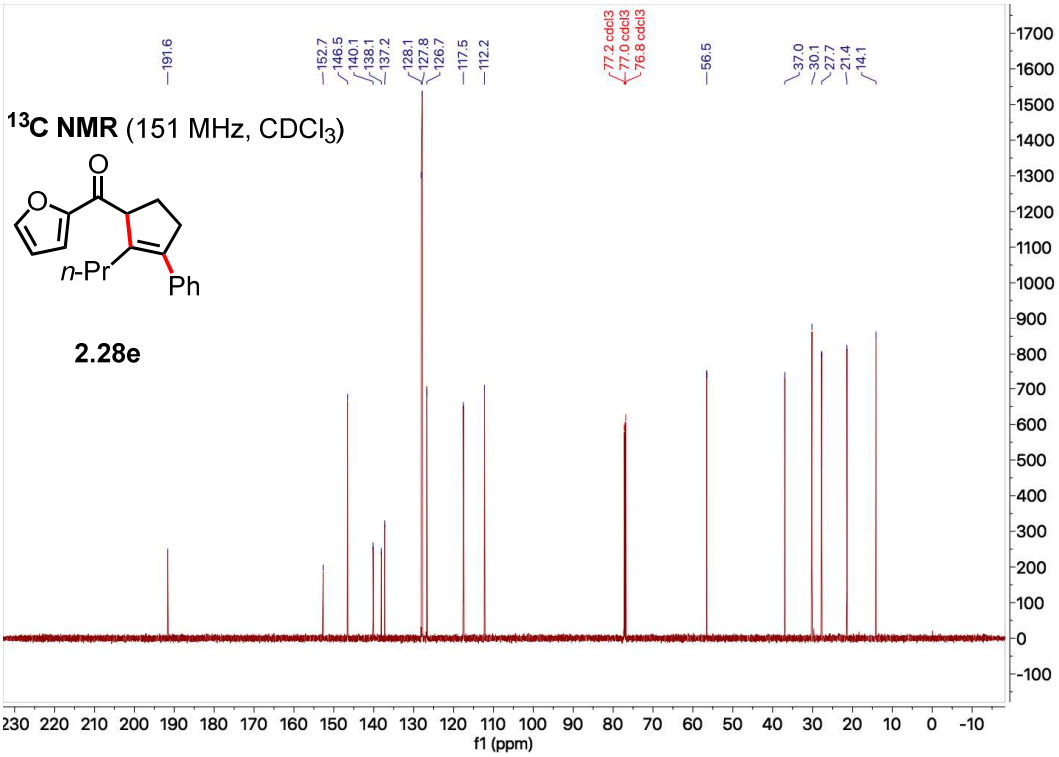

8.49 8.03 8.01 7.91 7.89 7.85 7.83 7.81 7.79 7.54 7.52 7.51 7.49 7.47 7.46 7.29 7.28 7.20 7.19 7.18 7.17 7.16 7.14 4.69 4.68 4.66 2.84 2.82 2.42 2.40 2.38 2.35 2.33 2.14 2.13 2.11 2.09 2.08 2.06 1.75
1H NMR (400 MHz, CDCl3)
O
Me
Ph
2.28c
1.00 1.02 1.04 2.07 2.11 4.02 1.27 1.02 2.06 1.07 1.08 3.12
f1 (ppm)

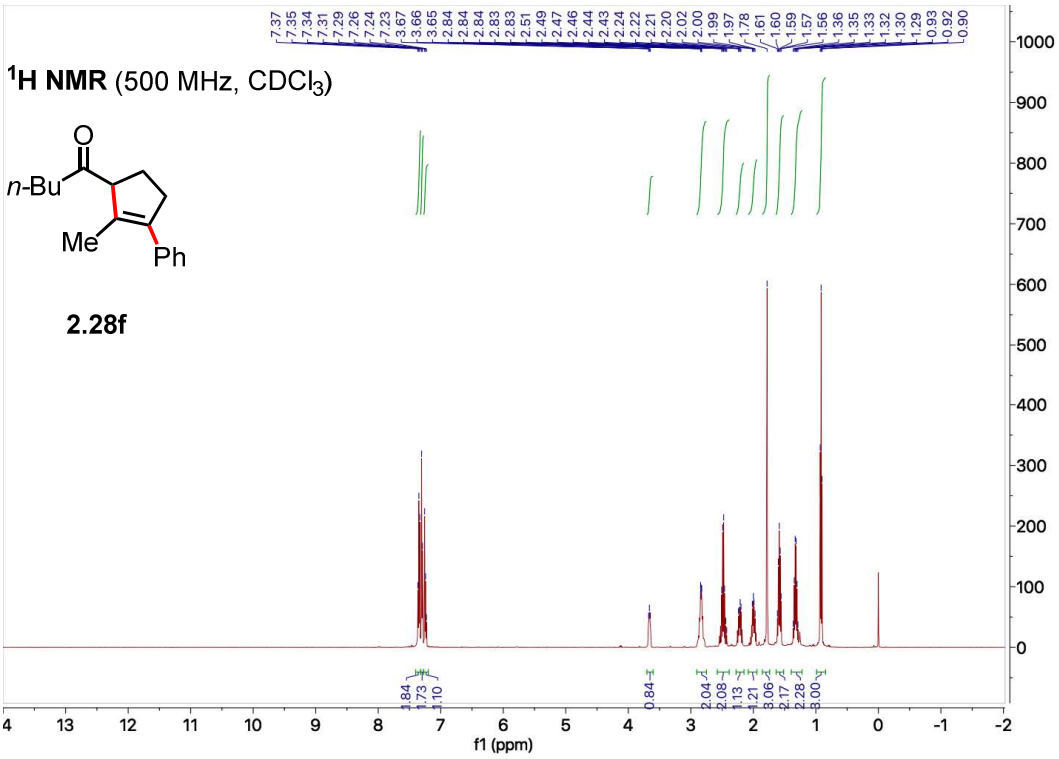

202.2 139.1 137.8 135.5 134.5 133.2 132.6 130.2 129.6 128.5 128.4 128.1 127.9 127.7 126.7 126.6 124.3 77.2 cdcl3 77.0 cdcl3 76.8 cdcl3 58.9 36.4 27.8 14.9
13C NMR (126 MHz, CDCl3)
O
Me
Ph
2.28c
f1 (ppm)

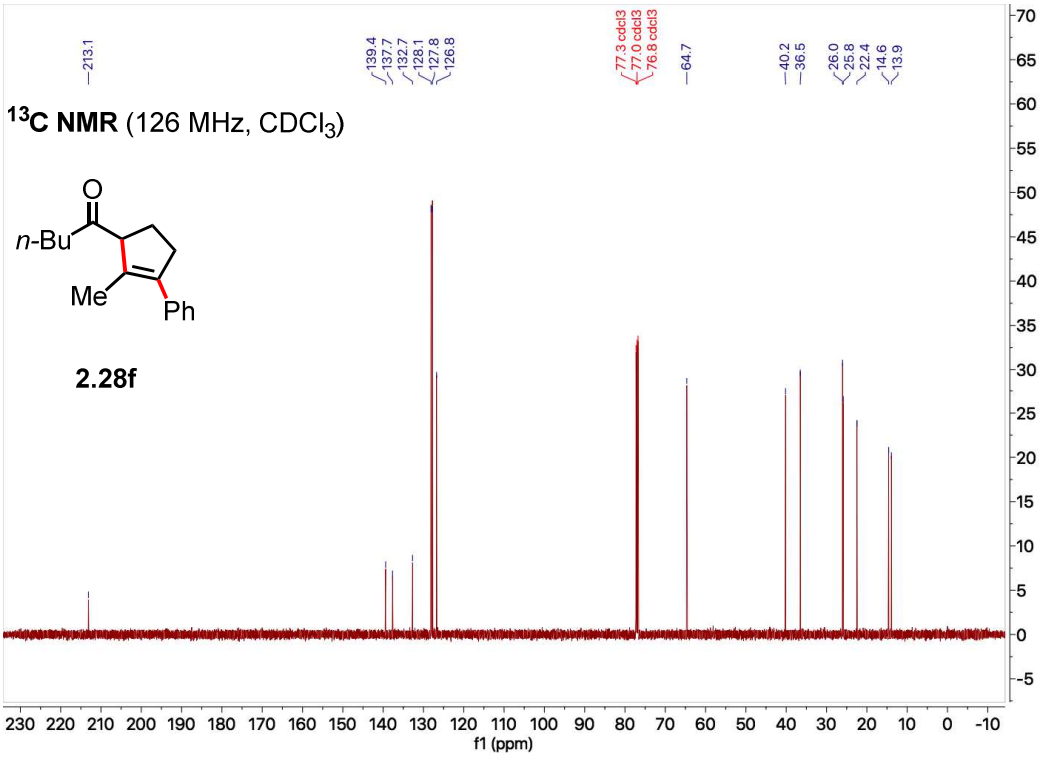

7.58 7.55 7.46 7.44 7.42 7.35 7.33 7.31 7.29 7.27 7.24 7.22 7.20 7.02 7.00 6.98 6.96 4.71 4.69 4.68 3.90 2.82 2.80 2.80 2.73 2.72 2.72 2.70 2.37 2.37 2.36 2.35 2.26 2.26 2.24 2.12 2.10 2.08 2.06 1.37 1.37 1.36 1.35 1.35 1.34 1.26 1.25 1.24 1.23 1.23 1.22 1.22 1.21 1.20 1.19 1.18 1.16 1.14 0.78 0.76 0.74
1H NMR (600 MHz, CDCl3)
MeO
O
n-Bu
Ph
2.28d
0.95 0.98 3.97 1.06 1.99 0.98 3.04 1.03 1.01 2.10 2.08 4.47 3.00
f1 (ppm)

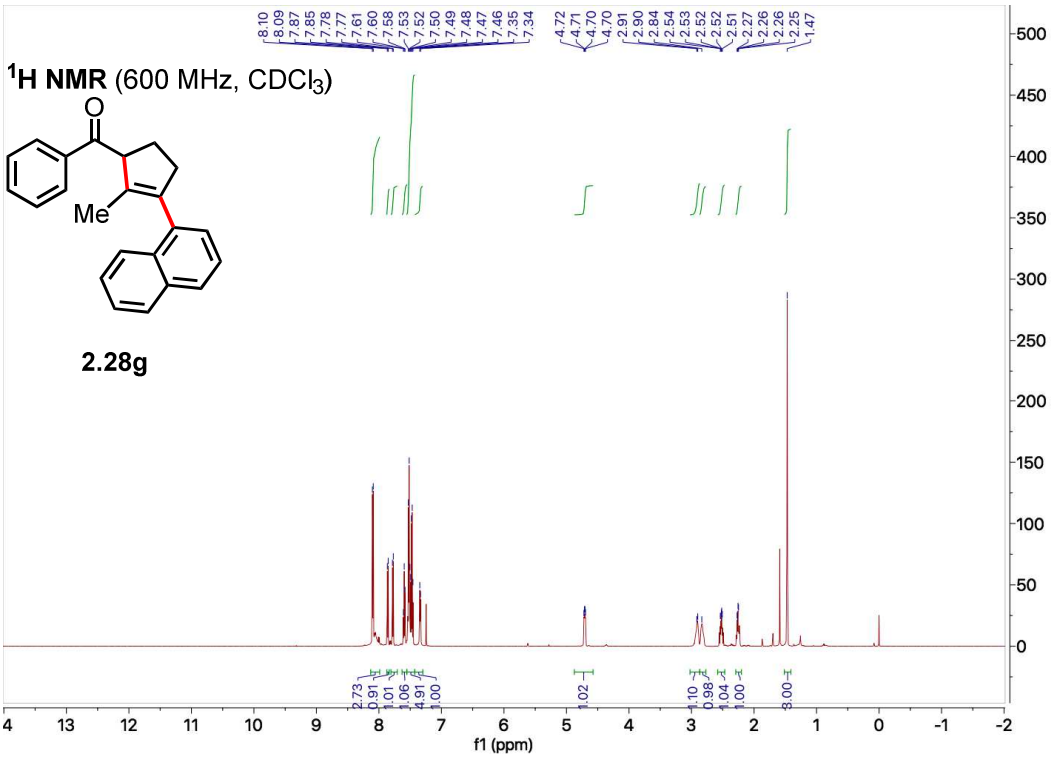

205.96 157.91 139.21 138.39 138.38 132.78 129.88 129.78 127.96 127.86 126.42 120.67 111.40 77.32 CDCl3 77.00 cdcl3 76.68 CDCl3 59.94 55.46 36.55 30.25 27.87 27.62 22.69 13.81
13C NMR (101 MHz, CDCl3)
MeO
O
n-Bu
Ph
2.28d
f1 (ppm)


1H NMR (600 MHz, CDCl3)
n-Pr
Ph
2.28e
f1 (ppm)


13C NMR (151 MHz, CDCl3)
n-Pr
Ph
2.28e
f1 (ppm)

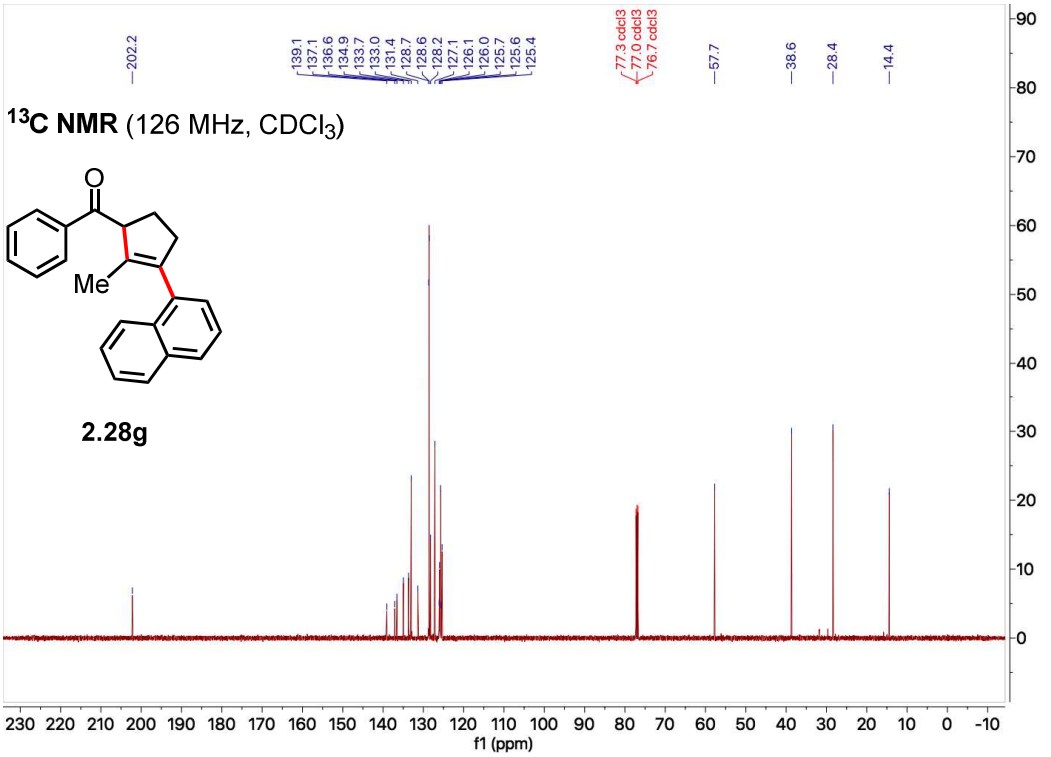

7.37
7.35
7.34
7.31
7.29
7.26
7.24
7.23
3.67
3.66
3.65
2.84
2.84
2.84
2.83
2.83
2.51
2.49
2.47
2.46
2.44
2.43
2.24
2.22
2.21
2.20
2.02
2.00
1.99
1.97
1.78
1.61
1.60
1.59
1.57
1.56
1.36
1.35
1.33
1.32
1.30
1.29
0.93
0.92
0.90
1H NMR (500 MHz, CDCl3)
n-Bu
Me
Ph
2.28f
1.84
1.73
1.10
0.84
2.04
2.08
2.13
3.21
8.06
2.17
2.28
3.00
f1 (ppm)


213.1
139.4
137.7
132.7
128.1
127.8
126.8
77.3 cdcl3
77.0 cdcl3
76.8 cdcl3
64.7
40.2
36.5
26.0
25.8
22.4
14.6
13.9
13C NMR (126 MHz, CDCl3)
n-Bu
Me
Ph
2.28f
f1 (ppm)



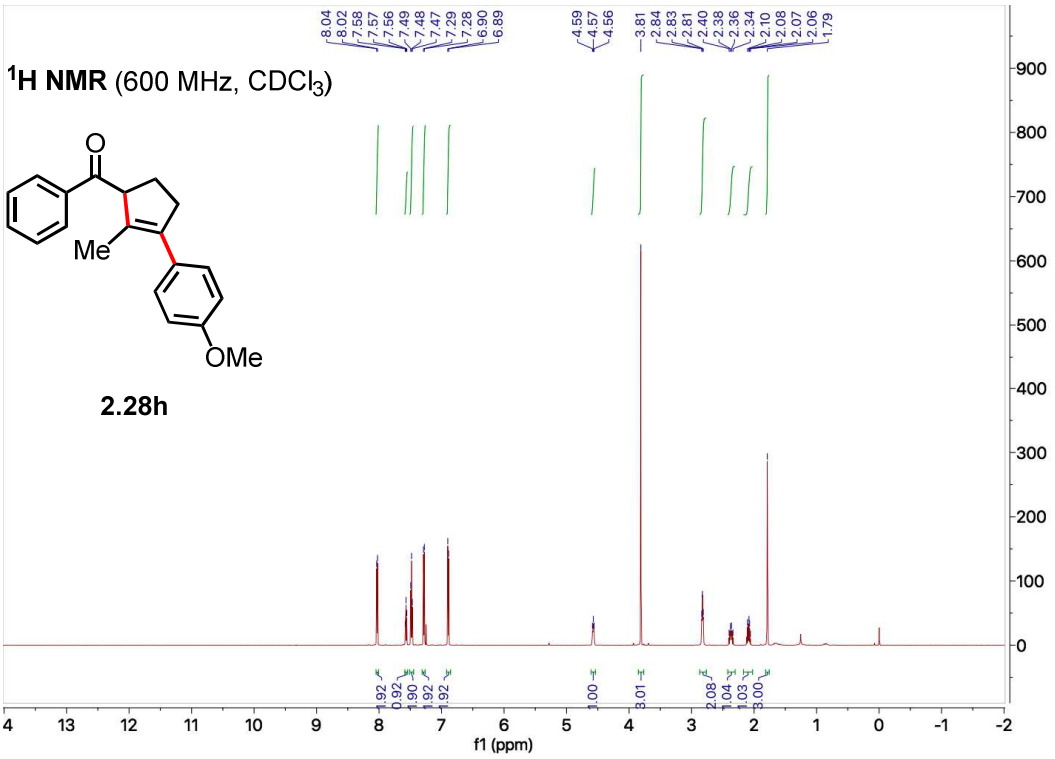
^{1}H NMR (600 MHz, $CDCl_3$)

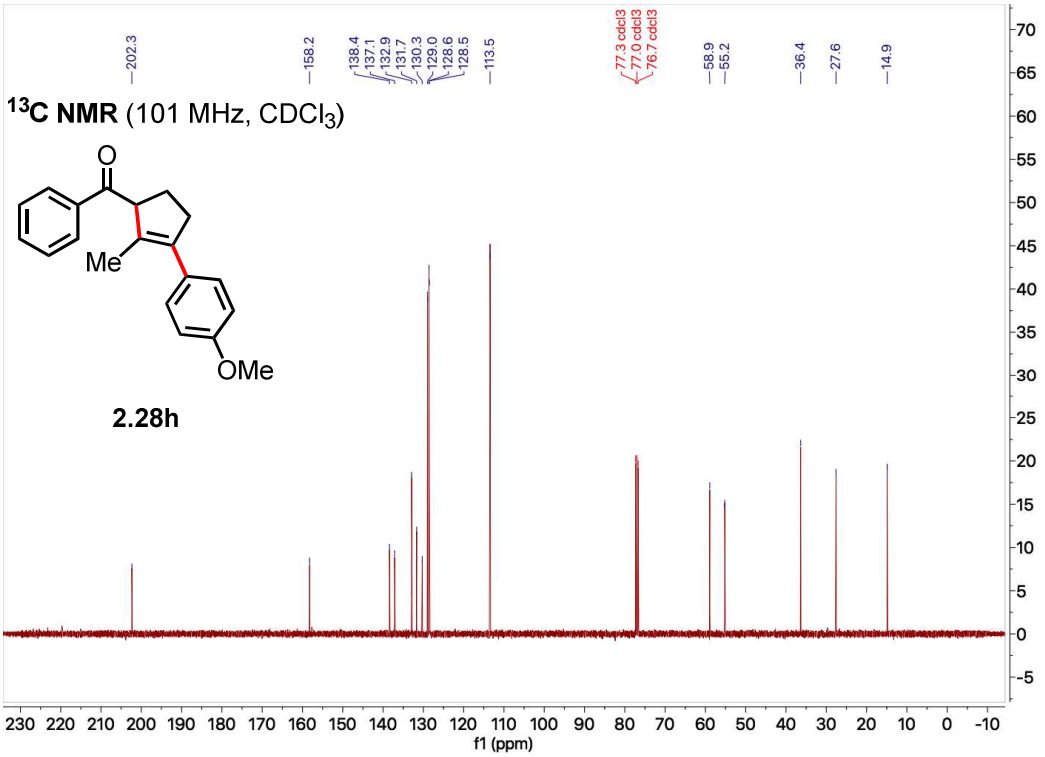
2.28g

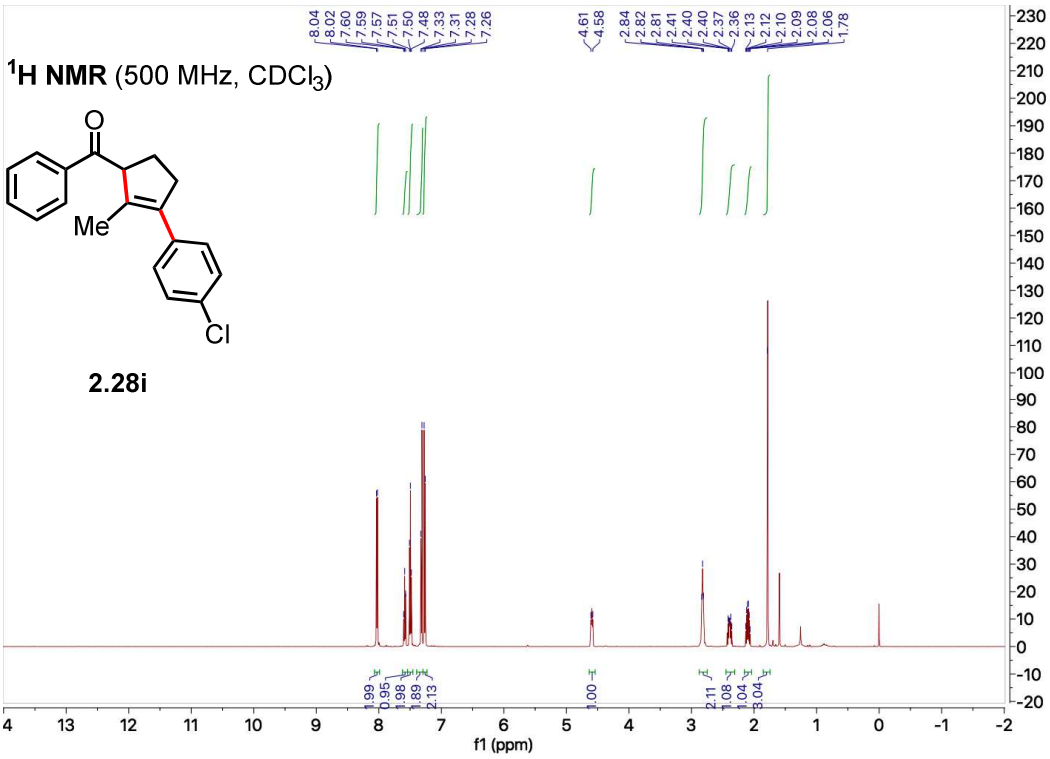


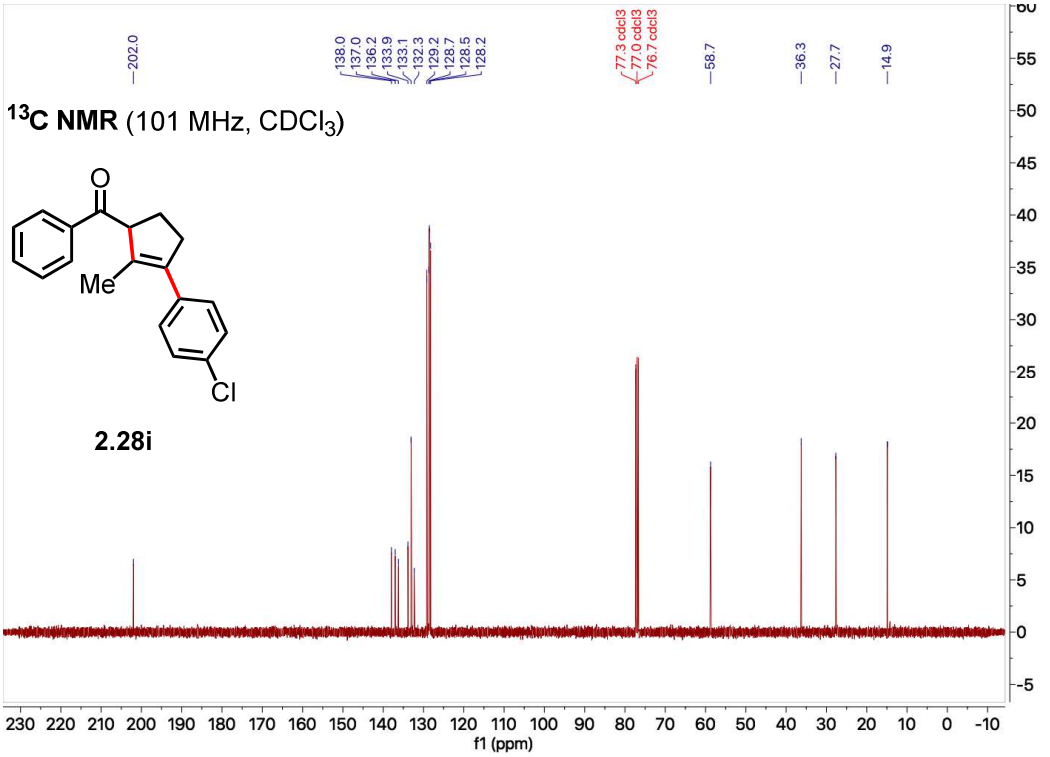
^{13}C NMR (126 MHz, $CDCl_3$)

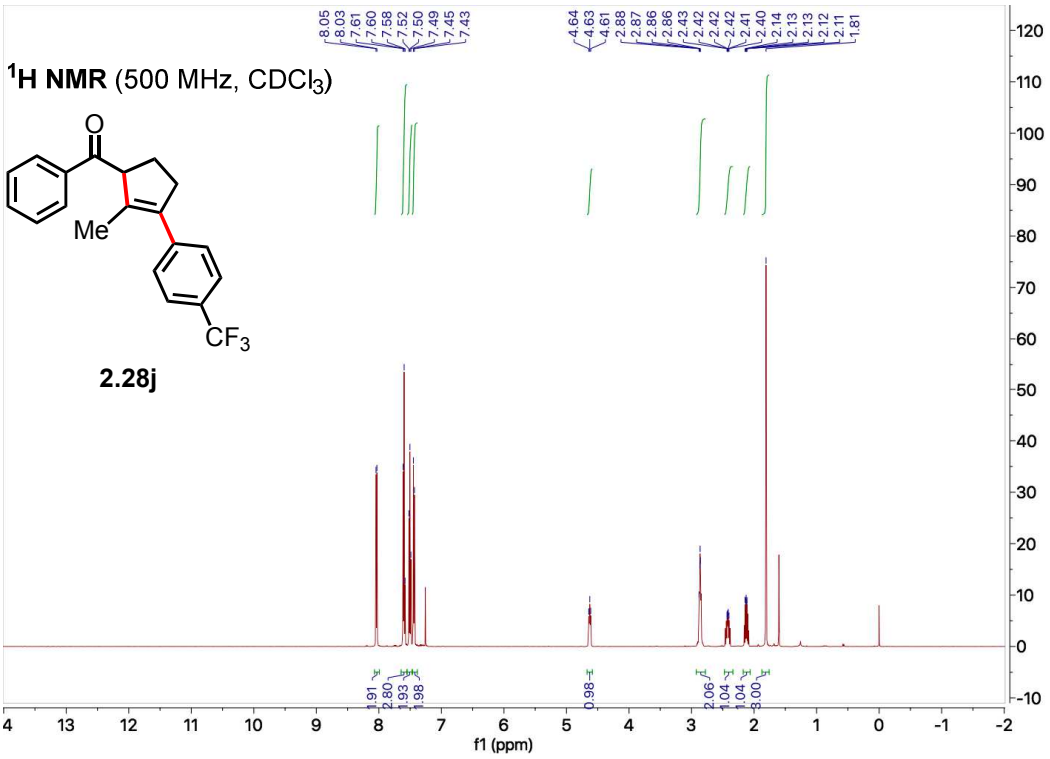
2.28g

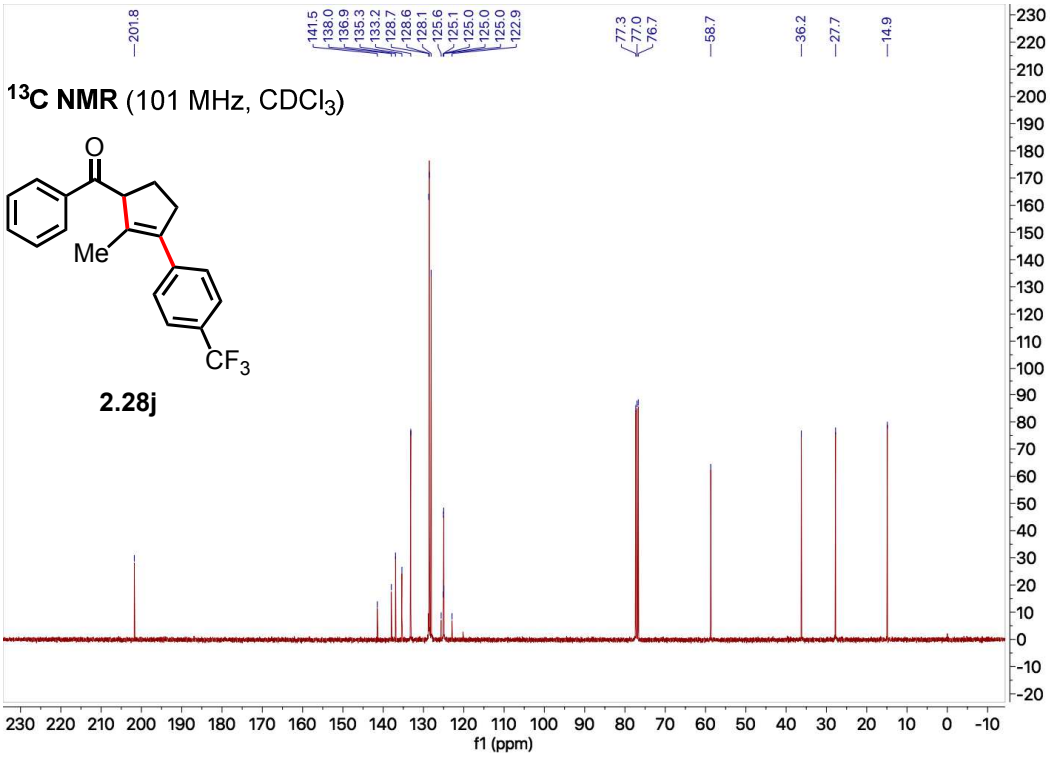

8.04
8.02
7.58
7.57
7.56
7.49
7.48
7.47
7.29
7.28
6.90
6.89
4.59
4.57
4.56
3.81
2.84
2.83
2.81
2.40
2.38
2.36
2.34
2.10
2.08
2.07
2.06
1.79
1H NMR (600 MHz, CDCl3)
Me
OMe
2.28h
1.92
0.92
1.90
1.92
1.92
1.00
3.01
2.08
1.04
1.03
3.00
f1 (ppm)

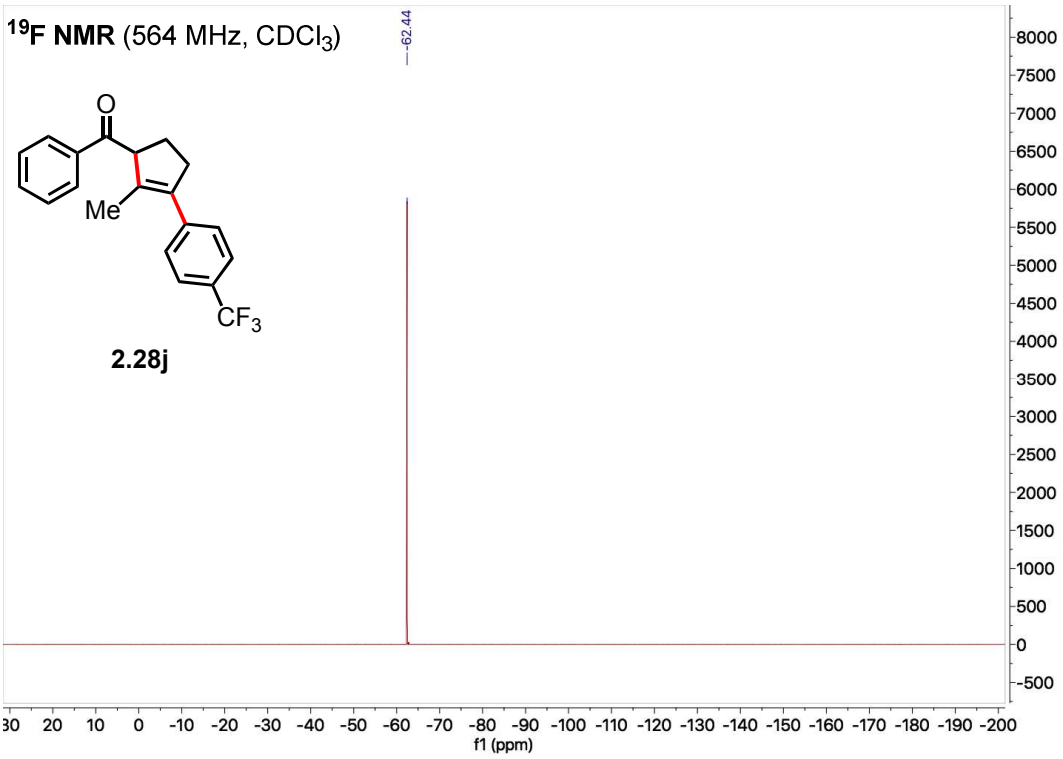

202.3
158.2
138.4
137.1
132.9
131.7
130.3
129.0
128.6
128.5
113.5
77.3 cdcl3
77.0 cdcl3
76.7 cdcl3
58.9
55.2
36.4
27.6
14.9
13C NMR (101 MHz, CDCl3)
Me
OMe
2.28h
f1 (ppm)

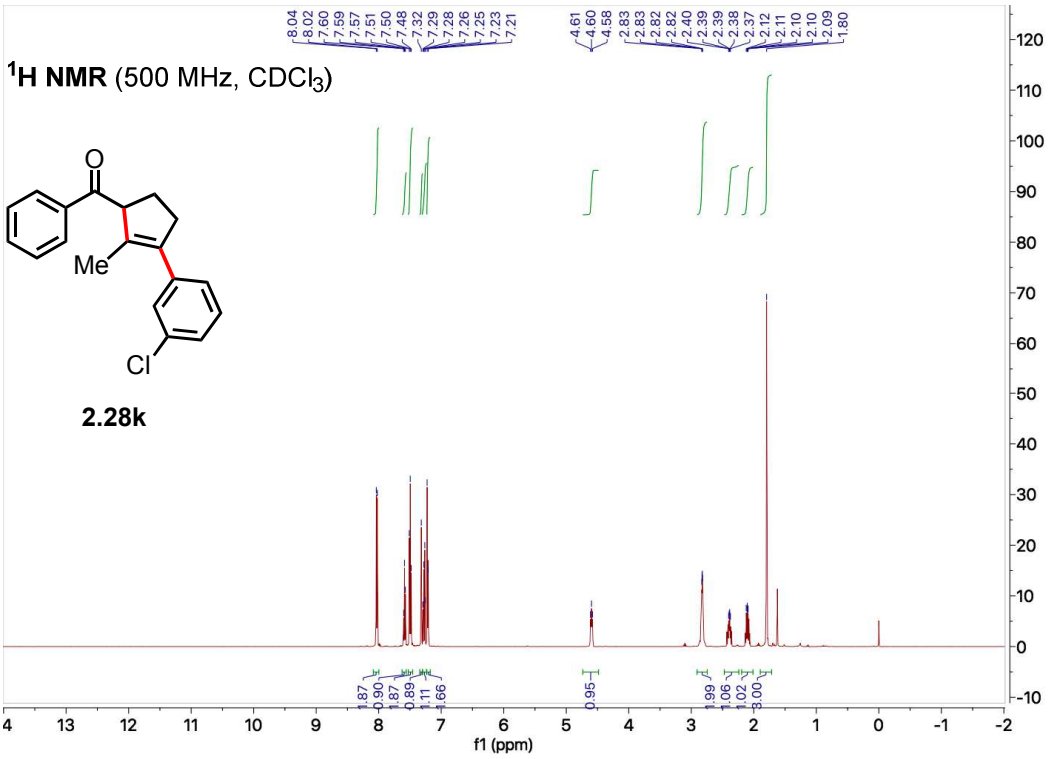

8.04
8.02
7.60
7.59
7.57
7.51
7.50
7.48
7.33
7.31
7.28
7.26
4.61
4.58
2.84
2.82
2.81
2.41
2.40
2.40
2.37
2.36
2.13
2.12
2.10
2.09
2.08
2.06
1.78
1H NMR (500 MHz, CDCl3)
O
Me
Cl
2.28i
1.99
0.95
1.98
1.89
2.13
1.00
2.11
1.08
1.04
3.04
f1 (ppm)

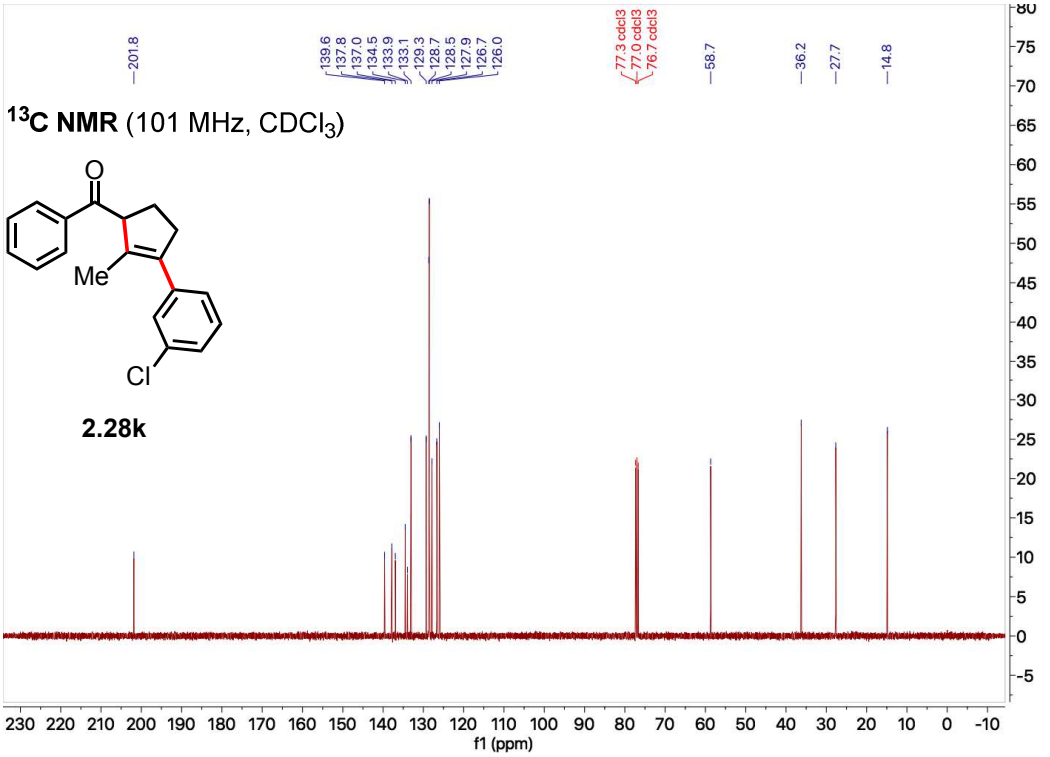

202.0
138.0
137.0
136.2
133.9
133.1
132.3
129.2
128.7
128.5
128.2
77.3 cdcl3
77.0 cdcl3
76.7 cdcl3
58.7
36.3
27.7
14.9
13C NMR (101 MHz, CDCl3)
O
Me
Cl
2.28i
f1 (ppm)

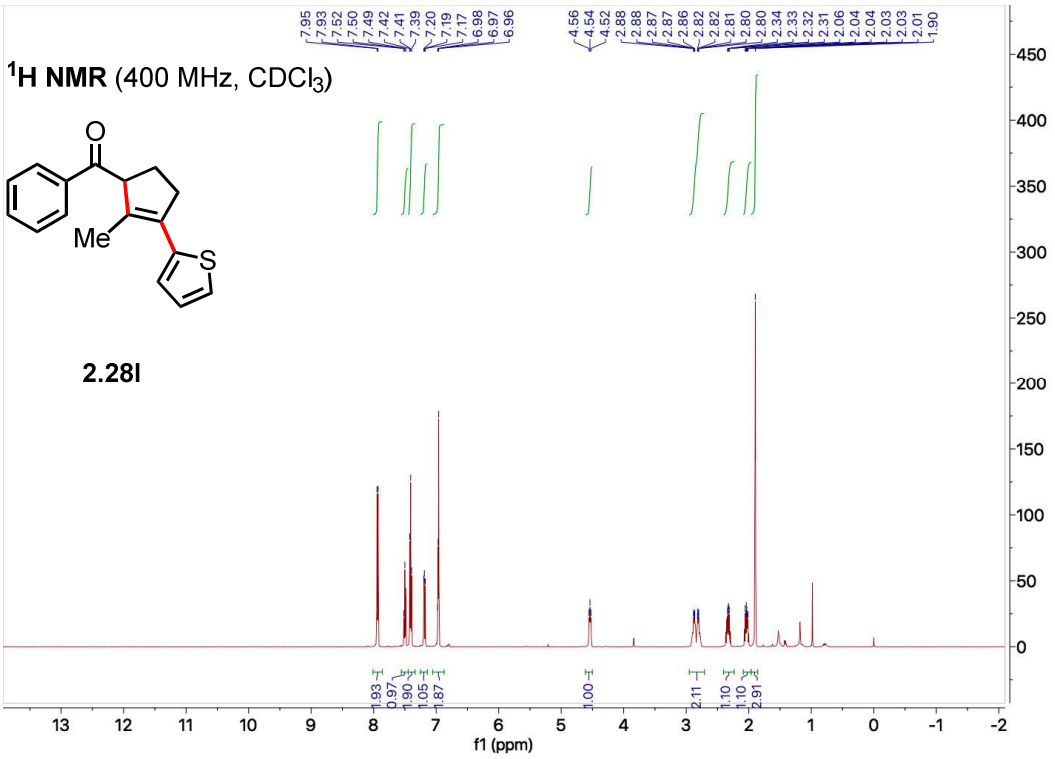

8.05
8.03
7.61
7.60
7.58
7.52
7.50
7.49
7.45
7.43
4.64
4.63
4.61
2.88
2.87
2.86
2.86
2.43
2.42
2.42
2.42
2.41
2.40
2.14
2.13
2.13
2.12
2.11
1.81
1H NMR (500 MHz, CDCl3)
O
Me
CF3
2.28j
1.91
2.80
1.93
1.98
0.98
2.06
1.04
1.04
3.00
f1 (ppm)

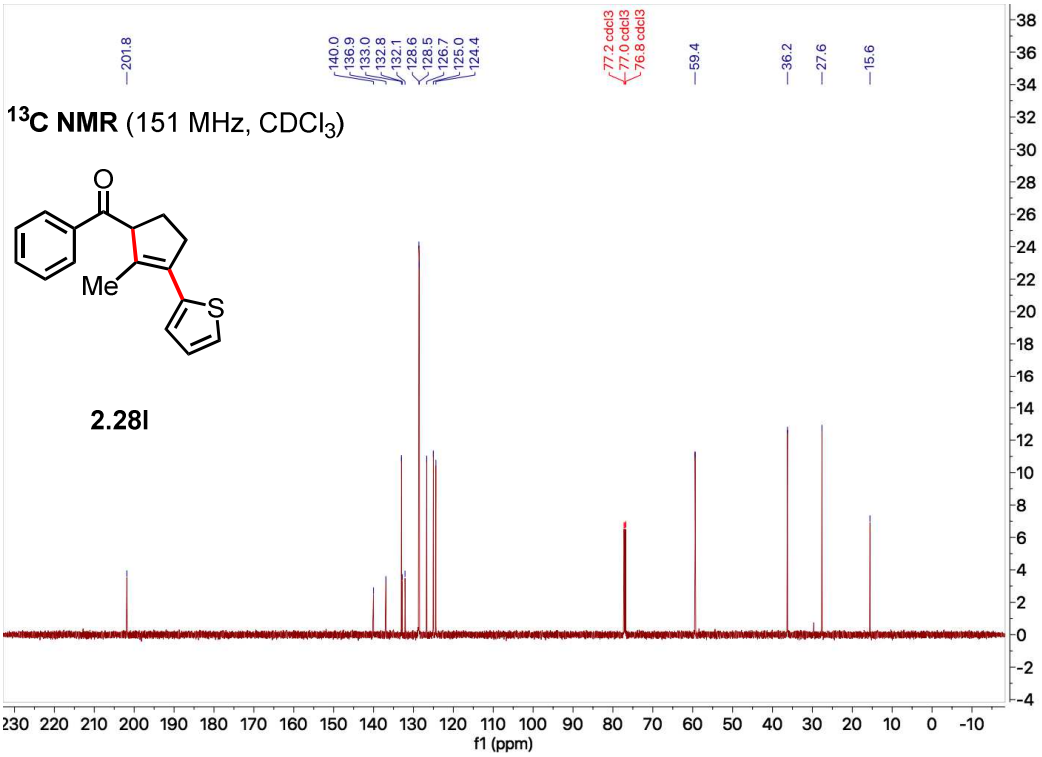

201.8
141.5
138.0
136.9
135.3
133.2
128.7
128.6
128.1
125.6
125.1
125.0
125.0
125.0
122.9
77.3
77.0
76.7
58.7
36.2
27.7
14.9
13C NMR (101 MHz, CDCl3)
O
Me
CF3
2.28j
f1 (ppm)


19F NMR (564 MHz, CDCl3)
-62.44
O
Me
CF3
2.28j
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


8.04
8.02
7.60
7.59
7.57
7.51
7.50
7.48
7.32
7.29
7.28
7.26
7.25
7.23
7.21
4.61
4.60
4.58
2.83
2.83
2.82
2.82
2.40
2.39
2.39
2.38
2.37
2.12
2.11
2.10
2.10
2.09
1.80
1H NMR (500 MHz, CDCl3)
O
Me
Cl
2.28k
1.87
0.90
1.87
0.89
1.11
1.66
0.95
1.99
1.06
1.02
3.00
f1 (ppm)


201.8
139.6
137.8
137.0
134.5
133.9
133.1
129.3
128.7
128.5
127.9
126.7
126.0
77.3 cdcl3
77.0 cdcl3
76.7 cdcl3
58.7
36.2
27.7
14.8
13C NMR (101 MHz, CDCl3)
O
Me
Cl
2.28k
f1 (ppm)


7.95
7.93
7.52
7.50
7.49
7.42
7.41
7.39
7.20
7.19
7.17
6.98
6.97
6.96
4.56
4.54
4.52
2.88
2.88
2.87
2.87
2.86
2.82
2.82
2.81
2.80
2.80
2.34
2.33
2.32
2.31
2.06
2.04
2.04
2.03
2.03
2.01
1.90
1H NMR (400 MHz, CDCl3)
O
Me
S
2.28l
1.93
0.97
1.90
1.05
1.87
1.00
2.11
1.10
1.10
2.91
f1 (ppm)


201.8
140.0
136.9
133.0
132.8
132.1
128.6
128.5
126.7
125.0
124.4
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
59.4
36.2
27.6
15.6
13C NMR (151 MHz, CDCl3)
O
Me
S
2.28l
f1 (ppm)

2.6.6 X-Ray Crystallography Data of 2.30c

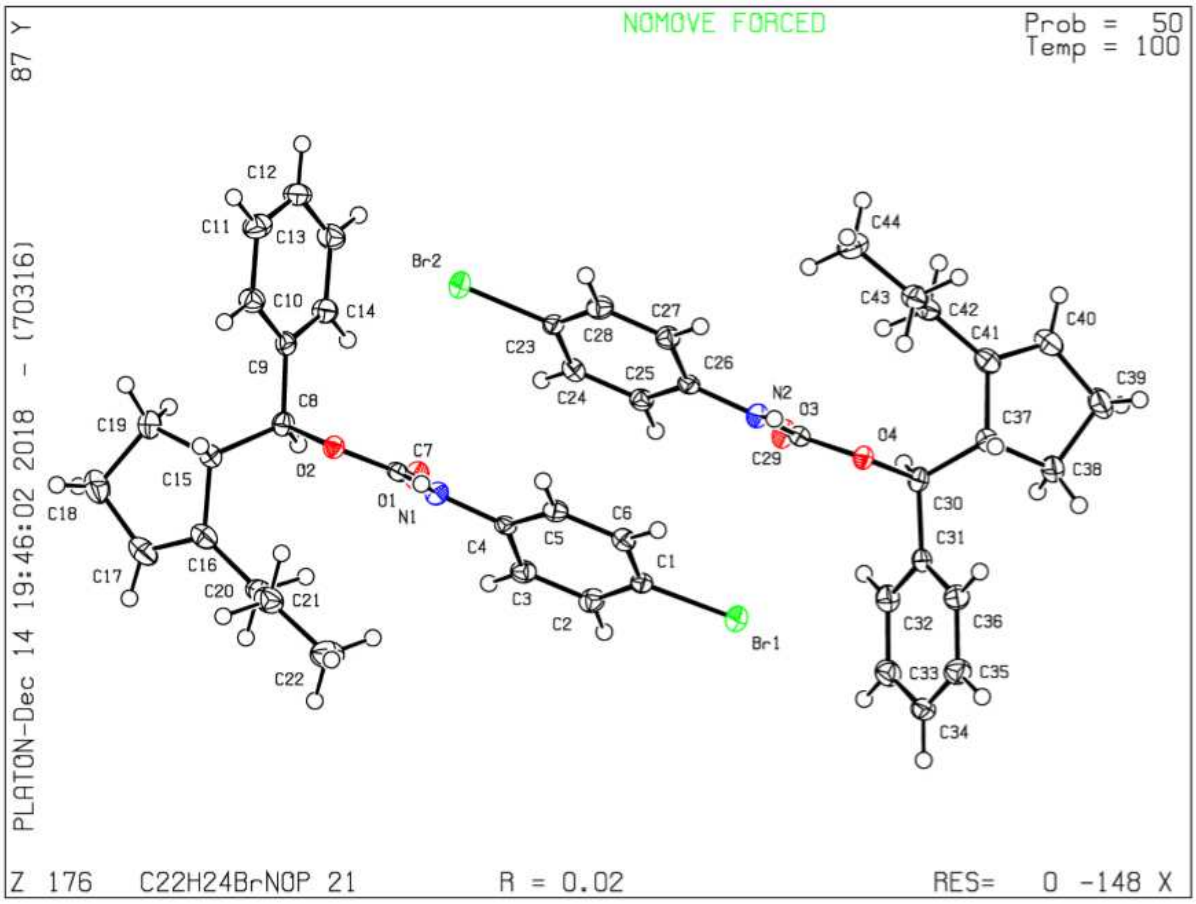


Table S1. Crystal data and structure refinement for $C_{22}H_{24}BrNO_2$.

Identification code	C22H24BrNO2
Empirical formula	C22 H24 Br N O2
Formula weight	414.33
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 5.1733(7) Å α= 90°.

	b = 21.213(3) Å β= 97.186(3)°.
	c = 17.838(2) Å γ = 90°.
Volume	1942.2(4) $Å^3$
Z	4
Density (calculated)	1.417 Mg/m^3
Absorption coefficient	3.002 mm^{-1}
F(000)	856
Crystal size	0.600 x 0.320 x 0.250 mm^3
Theta range for data collection	2.496 to 66.756°.
Index ranges	-6<=h<=6, -25<=k<=25, -20<=l<=21
Reflections collected	30083
Independent reflections	6781 [R(int) = 0.0411]
Completeness to theta = 66.756°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7528 and 0.4524
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6781 / 3 / 478
Goodness-of-fit on F^2	1.080
Final R indices [I>2sigma(I)]	R1 = 0.0220, wR2 = 0.0569
R indices (all data)	R1 = 0.0221, wR2 = 0.0570
Absolute structure parameter	0.021(12)
Extinction coefficient	n/a
Largest diff. peak and hole	0.369 and -0.319 $e.Å^{-3}$

Table S2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for $C_{22}H_{24}BrNO_2$. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	5552(1)	4272(1)	373(1)	27(1)
Br(2)	8026(1)	5755(1)	4587(1)	28(1)
N(1)	8293(4)	4037(1)	3778(1)	18(1)
N(2)	6281(4)	5943(1)	1162(1)	17(1)
O(1)	4149(4)	4070(1)	4106(1)	22(1)
O(2)	7713(4)	3972(1)	4984(1)	17(1)
O(3)	1851(4)	5883(1)	877(1)	21(1)
O(4)	4533(4)	6040(1)	-23(1)	17(1)
C(1)	6504(6)	4167(1)	1432(2)	19(1)
C(2)	4892(6)	3817(1)	1835(2)	22(1)
C(3)	5475(6)	3765(1)	2614(2)	21(1)
C(4)	7673(5)	4067(1)	2983(2)	16(1)
C(5)	9320(5)	4393(1)	2562(2)	19(1)
C(6)	8750(6)	4445(1)	1784(2)	21(1)
C(7)	6491(5)	4034(1)	4275(2)	17(1)
C(8)	6067(5)	3935(1)	5595(2)	18(1)
C(9)	6056(5)	4574(1)	5963(2)	18(1)
C(10)	8155(6)	4783(1)	6472(2)	23(1)

C(11)	8145(6)	5384(2)	6781(2)	27(1)
C(12)	6055(6)	5782(2)	6582(2)	26(1)
C(13)	3961(6)	5578(2)	6083(2)	27(1)
C(14)	3957(6)	4974(1)	5778(2)	23(1)
C(15)	7162(5)	3395(1)	6112(2)	20(1)
C(16)	6529(6)	2736(1)	5786(2)	24(1)
C(17)	5701(7)	2367(2)	6299(2)	31(1)
C(18)	5627(8)	2681(2)	7049(2)	38(1)
C(19)	5897(6)	3381(2)	6853(2)	26(1)
C(20)	6859(6)	2541(2)	4996(2)	26(1)
C(21)	9695(6)	2526(2)	4827(2)	29(1)
C(22)	9871(7)	2342(2)	4009(2)	36(1)
C(23)	7432(5)	5826(1)	3517(2)	18(1)
C(24)	5238(6)	5543(1)	3130(2)	20(1)
C(25)	4809(5)	5585(1)	2349(2)	19(1)
C(26)	6541(5)	5909(1)	1959(2)	16(1)
C(27)	8711(5)	6201(1)	2359(2)	20(1)
C(28)	9153(6)	6160(1)	3142(2)	22(1)
C(29)	4005(5)	5944(1)	689(2)	17(1)
C(30)	2302(5)	6083(1)	-624(2)	18(1)
C(31)	2150(5)	5466(1)	-1050(2)	18(1)
C(32)	341(6)	5017(2)	-893(2)	23(1)
C(33)	224(6)	4438(2)	-1259(2)	27(1)

C(34)	1896(6)	4309(2)	-1788(2)	25(1)
C(35)	3688(6)	4754(2)	-1950(2)	26(1)
C(36)	3833(6)	5330(1)	-1578(2)	23(1)
C(37)	2767(5)	6672(1)	-1085(2)	20(1)
C(38)	830(6)	6705(1)	-1822(2)	26(1)
C(39)	161(8)	7410(2)	-1942(2)	36(1)
C(40)	850(6)	7676(2)	-1166(2)	28(1)
C(41)	2246(5)	7290(1)	-694(2)	22(1)
C(42)	3279(6)	7452(1)	107(2)	23(1)
C(43)	6244(6)	7513(2)	256(2)	25(1)
C(44)	7136(7)	7665(2)	1081(2)	33(1)

Table S3. Bond lengths [Å] and angles [°] for $C_{22}H_{24}BrNO_2$.

Br(1)-C(1)	1.904(3)
Br(2)-C(23)	1.901(3)
N(1)-C(7)	1.364(4)
N(1)-C(4)	1.417(4)
N(1)-H(1N)	0.89(2)
N(2)-C(29)	1.360(4)
N(2)-C(26)	1.414(4)
N(2)-H(2N)	0.86(2)
O(1)-C(7)	1.214(4)
O(2)-C(7)	1.347(3)
O(2)-C(8)	1.468(3)
O(3)-C(29)	1.210(3)
O(4)-C(29)	1.348(3)
O(4)-C(30)	1.476(3)
C(1)-C(6)	1.382(4)
C(1)-C(2)	1.384(4)
C(2)-C(3)	1.389(4)
C(2)-H(2)	0.9500
C(3)-C(4)	1.395(4)
C(3)-H(3)	0.9500
C(4)-C(5)	1.389(4)
C(5)-C(6)	1.387(4)

C(5)-H(5)	0.9500
C(6)-H(6)	0.9500
C(8)-C(9)	1.506(4)
C(8)-C(15)	1.534(4)
C(8)-H(8)	1.0000
C(9)-C(14)	1.385(4)
C(9)-C(10)	1.397(4)
C(10)-C(11)	1.388(4)
C(10)-H(10)	0.9500
C(11)-C(12)	1.384(5)
C(11)-H(11)	0.9500
C(12)-C(13)	1.383(5)
C(12)-H(12)	0.9500
C(13)-C(14)	1.392(4)
C(13)-H(13)	0.9500
C(14)-H(14)	0.9500
C(15)-C(16)	1.532(4)
C(15)-C(19)	1.548(4)
C(15)-H(15)	1.0000
C(16)-C(17)	1.317(5)
C(16)-C(20)	1.499(4)
C(17)-C(18)	1.498(5)
C(17)-H(17)	0.9500

C(18)-C(19)	1.535(5)
C(18)-H(18A)	0.9900
C(18)-H(18B)	0.9900
C(19)-H(19A)	0.9900
C(19)-H(19B)	0.9900
C(20)-C(21)	1.535(4)
C(20)-H(20A)	0.9900
C(20)-H(20B)	0.9900
C(21)-C(22)	1.524(5)
C(21)-H(21A)	0.9900
C(21)-H(21B)	0.9900
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(23)-C(28)	1.375(4)
C(23)-C(24)	1.389(4)
C(24)-C(25)	1.387(4)
C(24)-H(24)	0.9500
C(25)-C(26)	1.383(4)
C(25)-H(25)	0.9500
C(26)-C(27)	1.397(4)
C(27)-C(28)	1.388(4)
C(27)-H(27)	0.9500

C(28)-H(28)	0.9500
C(30)-C(31)	1.511(4)
C(30)-C(37)	1.532(4)
C(30)-H(30)	1.0000
C(31)-C(32)	1.387(4)
C(31)-C(36)	1.391(4)
C(32)-C(33)	1.391(5)
C(32)-H(32)	0.9500
C(33)-C(34)	1.384(5)
C(33)-H(33)	0.9500
C(34)-C(35)	1.378(5)
C(34)-H(34)	0.9500
C(35)-C(36)	1.388(4)
C(35)-H(35)	0.9500
C(36)-H(36)	0.9500
C(37)-C(41)	1.525(4)
C(37)-C(38)	1.551(4)
C(37)-H(37)	1.0000
C(38)-C(39)	1.544(4)
C(38)-H(38A)	0.9900
C(38)-H(38B)	0.9900
C(39)-C(40)	1.494(5)
C(39)-H(39A)	0.9900

C(39)-H(39B)	0.9900
C(40)-C(41)	1.322(4)
C(40)-H(40)	0.9500
C(41)-C(42)	1.502(4)
C(42)-C(43)	1.529(4)
C(42)-H(42A)	0.9900
C(42)-H(42B)	0.9900
C(43)-C(44)	1.521(4)
C(43)-H(43A)	0.9900
C(43)-H(43B)	0.9900
C(44)-H(44A)	0.9800
C(44)-H(44B)	0.9800
C(44)-H(44C)	0.9800

C(7)-N(1)-C(4)	124.2(2)
C(7)-N(1)-H(1N)	120(2)
C(4)-N(1)-H(1N)	116(2)
C(29)-N(2)-C(26)	126.2(2)
C(29)-N(2)-H(2N)	118(2)
C(26)-N(2)-H(2N)	115(2)
C(7)-O(2)-C(8)	117.0(2)
C(29)-O(4)-C(30)	117.4(2)
C(6)-C(1)-C(2)	121.3(3)

C(6)-C(1)-Br(1)	120.0(2)
C(2)-C(1)-Br(1)	118.7(2)
C(1)-C(2)-C(3)	119.5(3)
C(1)-C(2)-H(2)	120.2
C(3)-C(2)-H(2)	120.2
C(2)-C(3)-C(4)	119.9(3)
C(2)-C(3)-H(3)	120.1
C(4)-C(3)-H(3)	120.1
C(5)-C(4)-C(3)	119.5(3)
C(5)-C(4)-N(1)	119.1(2)
C(3)-C(4)-N(1)	121.4(3)
C(6)-C(5)-C(4)	120.8(3)
C(6)-C(5)-H(5)	119.6
C(4)-C(5)-H(5)	119.6
C(1)-C(6)-C(5)	118.9(3)
C(1)-C(6)-H(6)	120.5
C(5)-C(6)-H(6)	120.5
O(1)-C(7)-O(2)	125.1(3)
O(1)-C(7)-N(1)	125.6(3)
O(2)-C(7)-N(1)	109.3(2)
O(2)-C(8)-C(9)	108.1(2)
O(2)-C(8)-C(15)	106.3(2)
C(9)-C(8)-C(15)	115.6(2)

O(2)-C(8)-H(8)	108.9
C(9)-C(8)-H(8)	108.9
C(15)-C(8)-H(8)	108.9
C(14)-C(9)-C(10)	118.8(3)
C(14)-C(9)-C(8)	119.5(3)
C(10)-C(9)-C(8)	121.6(3)
C(11)-C(10)-C(9)	120.5(3)
C(11)-C(10)-H(10)	119.7
C(9)-C(10)-H(10)	119.7
C(12)-C(11)-C(10)	120.0(3)
C(12)-C(11)-H(11)	120.0
C(10)-C(11)-H(11)	120.0
C(13)-C(12)-C(11)	119.9(3)
C(13)-C(12)-H(12)	120.0
C(11)-C(12)-H(12)	120.0
C(12)-C(13)-C(14)	120.1(3)
C(12)-C(13)-H(13)	119.9
C(14)-C(13)-H(13)	119.9
C(9)-C(14)-C(13)	120.6(3)
C(9)-C(14)-H(14)	119.7
C(13)-C(14)-H(14)	119.7
C(16)-C(15)-C(8)	114.1(2)
C(16)-C(15)-C(19)	102.4(2)

C(8)-C(15)-C(19)	111.3(2)
C(16)-C(15)-H(15)	109.6
C(8)-C(15)-H(15)	109.6
C(19)-C(15)-H(15)	109.6
C(17)-C(16)-C(20)	125.1(3)
C(17)-C(16)-C(15)	110.6(3)
C(20)-C(16)-C(15)	124.3(3)
C(16)-C(17)-C(18)	113.7(3)
C(16)-C(17)-H(17)	123.1
C(18)-C(17)-H(17)	123.1
C(17)-C(18)-C(19)	102.4(3)
C(17)-C(18)-H(18A)	111.3
C(19)-C(18)-H(18A)	111.3
C(17)-C(18)-H(18B)	111.3
C(19)-C(18)-H(18B)	111.3
H(18A)-C(18)-H(18B)	109.2
C(18)-C(19)-C(15)	105.8(3)
C(18)-C(19)-H(19A)	110.6
C(15)-C(19)-H(19A)	110.6
C(18)-C(19)-H(19B)	110.6
C(15)-C(19)-H(19B)	110.6
H(19A)-C(19)-H(19B)	108.7
C(16)-C(20)-C(21)	114.5(3)

C(16)-C(20)-H(20A)	108.6
C(21)-C(20)-H(20A)	108.6
C(16)-C(20)-H(20B)	108.6
C(21)-C(20)-H(20B)	108.6
H(20A)-C(20)-H(20B)	107.6
C(22)-C(21)-C(20)	111.5(3)
C(22)-C(21)-H(21A)	109.3
C(20)-C(21)-H(21A)	109.3
C(22)-C(21)-H(21B)	109.3
C(20)-C(21)-H(21B)	109.3
H(21A)-C(21)-H(21B)	108.0
C(21)-C(22)-H(22A)	109.5
C(21)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
C(21)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
C(28)-C(23)-C(24)	121.3(3)
C(28)-C(23)-Br(2)	119.8(2)
C(24)-C(23)-Br(2)	118.9(2)
C(25)-C(24)-C(23)	119.3(3)
C(25)-C(24)-H(24)	120.4
C(23)-C(24)-H(24)	120.4

C(26)-C(25)-C(24)	120.3(3)
C(26)-C(25)-H(25)	119.8
C(24)-C(25)-H(25)	119.8
C(25)-C(26)-C(27)	119.5(3)
C(25)-C(26)-N(2)	123.0(2)
C(27)-C(26)-N(2)	117.4(2)
C(28)-C(27)-C(26)	120.5(3)
C(28)-C(27)-H(27)	119.8
C(26)-C(27)-H(27)	119.8
C(23)-C(28)-C(27)	119.1(3)
C(23)-C(28)-H(28)	120.5
C(27)-C(28)-H(28)	120.5
O(3)-C(29)-O(4)	125.4(2)
O(3)-C(29)-N(2)	125.7(3)
O(4)-C(29)-N(2)	108.8(2)
O(4)-C(30)-C(31)	107.3(2)
O(4)-C(30)-C(37)	106.2(2)
C(31)-C(30)-C(37)	116.0(2)
O(4)-C(30)-H(30)	109.0
C(31)-C(30)-H(30)	109.0
C(37)-C(30)-H(30)	109.0
C(32)-C(31)-C(36)	119.3(3)
C(32)-C(31)-C(30)	119.1(3)

C(36)-C(31)-C(30)	121.5(3)
C(31)-C(32)-C(33)	120.2(3)
C(31)-C(32)-H(32)	119.9
C(33)-C(32)-H(32)	119.9
C(34)-C(33)-C(32)	120.0(3)
C(34)-C(33)-H(33)	120.0
C(32)-C(33)-H(33)	120.0
C(35)-C(34)-C(33)	120.2(3)
C(35)-C(34)-H(34)	119.9
C(33)-C(34)-H(34)	119.9
C(34)-C(35)-C(36)	120.0(3)
C(34)-C(35)-H(35)	120.0
C(36)-C(35)-H(35)	120.0
C(35)-C(36)-C(31)	120.3(3)
C(35)-C(36)-H(36)	119.8
C(31)-C(36)-H(36)	119.8
C(41)-C(37)-C(30)	114.0(2)
C(41)-C(37)-C(38)	102.5(2)
C(30)-C(37)-C(38)	111.3(2)
C(41)-C(37)-H(37)	109.6
C(30)-C(37)-H(37)	109.6
C(38)-C(37)-H(37)	109.6
C(39)-C(38)-C(37)	105.7(2)

C(39)-C(38)-H(38A)	110.6
C(37)-C(38)-H(38A)	110.6
C(39)-C(38)-H(38B)	110.6
C(37)-C(38)-H(38B)	110.6
H(38A)-C(38)-H(38B)	108.7
C(40)-C(39)-C(38)	102.3(3)
C(40)-C(39)-H(39A)	111.3
C(38)-C(39)-H(39A)	111.3
C(40)-C(39)-H(39B)	111.3
C(38)-C(39)-H(39B)	111.3
H(39A)-C(39)-H(39B)	109.2
C(41)-C(40)-C(39)	113.9(3)
C(41)-C(40)-H(40)	123.1
C(39)-C(40)-H(40)	123.1
C(40)-C(41)-C(42)	124.5(3)
C(40)-C(41)-C(37)	110.7(3)
C(42)-C(41)-C(37)	124.7(3)
C(41)-C(42)-C(43)	114.5(2)
C(41)-C(42)-H(42A)	108.6
C(43)-C(42)-H(42A)	108.6
C(41)-C(42)-H(42B)	108.6
C(43)-C(42)-H(42B)	108.6
H(42A)-C(42)-H(42B)	107.6

C(44)-C(43)-C(42)	111.2(3)
C(44)-C(43)-H(43A)	109.4
C(42)-C(43)-H(43A)	109.4
C(44)-C(43)-H(43B)	109.4
C(42)-C(43)-H(43B)	109.4
H(43A)-C(43)-H(43B)	108.0
C(43)-C(44)-H(44A)	109.5
C(43)-C(44)-H(44B)	109.5
H(44A)-C(44)-H(44B)	109.5
C(43)-C(44)-H(44C)	109.5
H(44A)-C(44)-H(44C)	109.5
H(44B)-C(44)-H(44C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table S4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for $C_{22}H_{24}BrNO_2$. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	37(1)	24(1)	18(1)	1(1)	-3(1)	-1(1)
Br(2)	39(1)	26(1)	16(1)	2(1)	-2(1)	-2(1)
N(1)	15(1)	20(1)	18(1)	-1(1)	1(1)	-1(1)
N(2)	15(1)	21(1)	16(1)	1(1)	4(1)	-1(1)
O(1)	16(1)	29(1)	21(1)	1(1)	1(1)	1(1)
O(2)	16(1)	18(1)	16(1)	1(1)	2(1)	-1(1)
O(3)	16(1)	31(1)	18(1)	2(1)	3(1)	0(1)
O(4)	16(1)	20(1)	14(1)	1(1)	0(1)	-1(1)
C(1)	25(1)	15(1)	17(1)	-2(1)	1(1)	5(1)
C(2)	19(1)	23(2)	21(1)	-2(1)	-2(1)	0(1)
C(3)	20(1)	19(1)	23(2)	-2(1)	5(1)	-2(1)
C(4)	17(1)	12(1)	18(1)	-1(1)	0(1)	4(1)
C(5)	17(1)	18(2)	22(1)	-2(1)	2(1)	-1(1)
C(6)	24(1)	17(1)	21(1)	1(1)	4(1)	-2(1)
C(7)	19(1)	11(1)	19(1)	0(1)	1(1)	0(1)
C(8)	18(1)	21(1)	17(1)	1(1)	4(1)	1(1)
C(9)	20(1)	19(1)	16(1)	2(1)	4(1)	-2(1)
C(10)	22(1)	21(1)	25(2)	-1(1)	1(1)	-1(1)

C(11)	28(2)	26(2)	27(2)	-6(1)	2(1)	-6(1)
C(12)	35(2)	19(1)	27(2)	-4(1)	10(1)	-3(1)
C(13)	29(2)	22(2)	29(2)	0(1)	6(1)	6(1)
C(14)	23(1)	22(2)	24(2)	-1(1)	2(1)	1(1)
C(15)	22(1)	17(1)	20(1)	2(1)	2(1)	0(1)
C(16)	23(1)	18(1)	30(2)	2(1)	1(1)	1(1)
C(17)	33(2)	19(2)	39(2)	6(1)	3(1)	-2(1)
C(18)	51(2)	31(2)	33(2)	11(2)	11(2)	-2(2)
C(19)	32(2)	26(2)	21(2)	4(1)	6(1)	-1(1)
C(20)	29(2)	16(1)	29(2)	-2(1)	-2(1)	0(1)
C(21)	29(2)	23(2)	34(2)	-1(1)	2(1)	6(1)
C(22)	40(2)	30(2)	39(2)	-7(2)	9(2)	2(2)
C(23)	24(1)	16(1)	15(1)	-2(1)	-1(1)	6(1)
C(24)	21(1)	16(1)	23(2)	3(1)	4(1)	0(1)
C(25)	19(1)	16(1)	21(1)	0(1)	-1(1)	-2(1)
C(26)	17(1)	13(1)	18(1)	-1(1)	2(1)	3(1)
C(27)	19(1)	19(1)	21(1)	-1(1)	2(1)	-2(1)
C(28)	18(1)	22(2)	24(2)	-4(1)	0(1)	-1(1)
C(29)	20(1)	13(1)	17(1)	0(1)	2(1)	1(1)
C(30)	16(1)	22(2)	15(1)	2(1)	1(1)	1(1)
C(31)	20(1)	17(1)	16(1)	2(1)	-2(1)	3(1)
C(32)	23(1)	25(2)	22(2)	3(1)	3(1)	2(1)
C(33)	30(2)	22(2)	27(2)	2(1)	-2(1)	-4(1)

C(34)	34(2)	17(1)	23(1)	-2(1)	-5(1)	4(1)
C(35)	28(2)	25(2)	25(2)	-3(1)	3(1)	6(1)
C(36)	22(1)	23(2)	23(2)	-1(1)	3(1)	0(1)
C(37)	22(1)	18(1)	20(1)	2(1)	2(1)	1(1)
C(38)	32(2)	22(2)	22(2)	3(1)	-2(1)	-1(1)
C(39)	48(2)	24(2)	32(2)	9(1)	-10(2)	-1(2)
C(40)	27(2)	19(2)	35(2)	3(1)	0(1)	0(1)
C(41)	19(1)	19(1)	27(2)	2(1)	5(1)	-3(1)
C(42)	28(2)	16(1)	24(2)	-1(1)	6(1)	2(1)
C(43)	29(2)	20(2)	26(2)	-1(1)	5(1)	-2(1)
C(44)	40(2)	30(2)	29(2)	-8(1)	-1(1)	-1(2)

Table S5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for $C_{22}H_{24}BrNO_2$.

	x	y	z	U(eq)
H(1N)	9980(50)	4058(16)	3953(18)	21
H(2N)	7700(50)	5998(17)	970(19)	21
H(2)	3396	3613	1581	26
H(3)	4380	3526	2895	25
H(5)	10855	4584	2811	23
H(6)	9885	4667	1498	25
H(8)	4249	3827	5374	22
H(10)	9600	4512	6608	27
H(11)	9574	5521	7129	33
H(12)	6059	6195	6787	32
H(13)	2521	5851	5948	32
H(14)	2503	4835	5440	27
H(15)	9092	3443	6232	24
H(17)	5197	1941	6204	37
H(18A)	7088	2539	7422	45
H(18B)	3960	2598	7249	45
H(19A)	7014	3602	7263	32
H(19B)	4168	3588	6781	32

H(20A)	5866	2837	4639	31
H(20B)	6092	2117	4902	31
H(21A)	10491	2946	4928	35
H(21B)	10691	2219	5168	35
H(22A)	9085	1925	3908	54
H(22B)	11703	2329	3922	54
H(22C)	8936	2653	3671	54
H(24)	4045	5323	3398	24
H(25)	3318	5391	2080	23
H(27)	9892	6428	2094	24
H(28)	10625	6360	3414	26
H(30)	667	6141	-386	21
H(32)	-821	5107	-534	28
H(33)	-1003	4129	-1147	32
H(34)	1807	3914	-2040	30
H(35)	4826	4666	-2315	31
H(36)	5087	5634	-1686	27
H(37)	4594	6670	-1214	24
H(38A)	1641	6536	-2254	31
H(38B)	-761	6458	-1769	31
H(39A)	1215	7605	-2306	43
H(39B)	-1711	7470	-2122	43
H(40)	332	8084	-1026	33

H(42A)	2716	7122	444	27
H(42B)	2490	7855	241	27
H(43A)	7056	7114	119	30
H(43B)	6826	7852	-67	30
H(44A)	6292	8053	1221	50
H(44B)	9031	7721	1155	50
H(44C)	6661	7317	1399	50

Table S6. Torsion angles [°] for $C_{22}H_{24}BrNO_2$.

C(6)-C(1)-C(2)-C(3)	2.8(4)
Br(1)-C(1)-C(2)-C(3)	-176.3(2)
C(1)-C(2)-C(3)-C(4)	0.1(4)
C(2)-C(3)-C(4)-C(5)	-2.8(4)
C(2)-C(3)-C(4)-N(1)	178.5(3)
C(7)-N(1)-C(4)-C(5)	145.5(3)
C(7)-N(1)-C(4)-C(3)	-35.8(4)
C(3)-C(4)-C(5)-C(6)	2.6(4)
N(1)-C(4)-C(5)-C(6)	-178.6(2)
C(2)-C(1)-C(6)-C(5)	-3.0(4)
Br(1)-C(1)-C(6)-C(5)	176.1(2)
C(4)-C(5)-C(6)-C(1)	0.2(4)
C(8)-O(2)-C(7)-O(1)	1.0(4)
C(8)-O(2)-C(7)-N(1)	-177.8(2)
C(4)-N(1)-C(7)-O(1)	-1.7(4)
C(4)-N(1)-C(7)-O(2)	177.0(2)
C(7)-O(2)-C(8)-C(9)	-100.4(3)
C(7)-O(2)-C(8)-C(15)	134.9(2)
O(2)-C(8)-C(9)-C(14)	100.3(3)
C(15)-C(8)-C(9)-C(14)	-140.8(3)
O(2)-C(8)-C(9)-C(10)	-77.7(3)
C(15)-C(8)-C(9)-C(10)	41.3(4)

C(14)-C(9)-C(10)-C(11)	-0.6(4)
C(8)-C(9)-C(10)-C(11)	177.4(3)
C(9)-C(10)-C(11)-C(12)	-0.5(5)
C(10)-C(11)-C(12)-C(13)	0.9(5)
C(11)-C(12)-C(13)-C(14)	-0.3(5)
C(10)-C(9)-C(14)-C(13)	1.2(4)
C(8)-C(9)-C(14)-C(13)	-176.9(3)
C(12)-C(13)-C(14)-C(9)	-0.7(5)
O(2)-C(8)-C(15)-C(16)	-74.6(3)
C(9)-C(8)-C(15)-C(16)	165.4(2)
O(2)-C(8)-C(15)-C(19)	170.1(2)
C(9)-C(8)-C(15)-C(19)	50.2(3)
C(8)-C(15)-C(16)-C(17)	-133.8(3)
C(19)-C(15)-C(16)-C(17)	-13.4(3)
C(8)-C(15)-C(16)-C(20)	47.2(4)
C(19)-C(15)-C(16)-C(20)	167.6(3)
C(20)-C(16)-C(17)-C(18)	178.4(3)
C(15)-C(16)-C(17)-C(18)	-0.6(4)
C(16)-C(17)-C(18)-C(19)	14.4(4)
C(17)-C(18)-C(19)-C(15)	-21.7(3)
C(16)-C(15)-C(19)-C(18)	21.5(3)
C(8)-C(15)-C(19)-C(18)	143.7(3)
C(17)-C(16)-C(20)-C(21)	-112.7(4)

C(15)-C(16)-C(20)-C(21)	66.2(4)
C(16)-C(20)-C(21)-C(22)	-178.4(3)
C(28)-C(23)-C(24)-C(25)	1.5(4)
Br(2)-C(23)-C(24)-C(25)	-179.1(2)
C(23)-C(24)-C(25)-C(26)	-0.3(4)
C(24)-C(25)-C(26)-C(27)	-0.9(4)
C(24)-C(25)-C(26)-N(2)	176.8(2)
C(29)-N(2)-C(26)-C(25)	32.0(4)
C(29)-N(2)-C(26)-C(27)	-150.3(3)
C(25)-C(26)-C(27)-C(28)	0.9(4)
N(2)-C(26)-C(27)-C(28)	-176.9(3)
C(24)-C(23)-C(28)-C(27)	-1.5(4)
Br(2)-C(23)-C(28)-C(27)	179.2(2)
C(26)-C(27)-C(28)-C(23)	0.3(4)
C(30)-O(4)-C(29)-O(3)	0.8(4)
C(30)-O(4)-C(29)-N(2)	-177.6(2)
C(26)-N(2)-C(29)-O(3)	-4.0(4)
C(26)-N(2)-C(29)-O(4)	174.4(2)
C(29)-O(4)-C(30)-C(31)	-103.7(3)
C(29)-O(4)-C(30)-C(37)	131.6(2)
O(4)-C(30)-C(31)-C(32)	100.5(3)
C(37)-C(30)-C(31)-C(32)	-140.9(3)
O(4)-C(30)-C(31)-C(36)	-77.5(3)

C(37)-C(30)-C(31)-C(36)	41.0(4)
C(36)-C(31)-C(32)-C(33)	0.3(4)
C(30)-C(31)-C(32)-C(33)	-177.8(3)
C(31)-C(32)-C(33)-C(34)	-0.7(4)
C(32)-C(33)-C(34)-C(35)	0.4(4)
C(33)-C(34)-C(35)-C(36)	0.4(4)
C(34)-C(35)-C(36)-C(31)	-0.9(4)
C(32)-C(31)-C(36)-C(35)	0.5(4)
C(30)-C(31)-C(36)-C(35)	178.6(3)
O(4)-C(30)-C(37)-C(41)	-75.1(3)
C(31)-C(30)-C(37)-C(41)	165.7(2)
O(4)-C(30)-C(37)-C(38)	169.6(2)
C(31)-C(30)-C(37)-C(38)	50.4(3)
C(41)-C(37)-C(38)-C(39)	21.0(3)
C(30)-C(37)-C(38)-C(39)	143.2(3)
C(37)-C(38)-C(39)-C(40)	-20.9(3)
C(38)-C(39)-C(40)-C(41)	13.5(4)
C(39)-C(40)-C(41)-C(42)	177.5(3)
C(39)-C(40)-C(41)-C(37)	0.1(4)
C(30)-C(37)-C(41)-C(40)	-133.9(3)
C(38)-C(37)-C(41)-C(40)	-13.5(3)
C(30)-C(37)-C(41)-C(42)	48.7(4)
C(38)-C(37)-C(41)-C(42)	169.1(3)

C(40)-C(41)-C(42)-C(43)	-111.9(3)
C(37)-C(41)-C(42)-C(43)	65.1(4)
C(41)-C(42)-C(43)-C(44)	-178.9(3)

Symmetry transformations used to generate equivalent atoms:

Table S7. Hydrogen bonds for $C_{22}H_{24}BrNO_2$ [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(1)#1	0.89(2)	2.14(2)	3.013(3)	167(3)
N(2)-H(2N)...O(3)#1	0.86(2)	2.19(3)	2.990(3)	156(3)

Symmetry transformations used to generate equivalent atoms:

#1 x+1,y,z

Chapter Three

Enantioselective Synthesis of *N*-Alkylamines through β-Amino C–H Functionalization Promoted by Cooperative Actions of $B(C_6F_5)_3$ and a Chiral Lewis Acid Co-Catalyst

Introduction

Synthesis of enantioenriched *N*-alkylamines through enantioselective transformations of α, β, γ, and/or δ-amino C–H bonds has emerged as an enabling approach to produce N-containing natural products and bioactive compounds (Scheme 3.1).[1-2] However, despite significant advances made in the development of C–H functionalization reactions, methods that allow for regio- and stereoselective late-stage C–H functionalization of bioactive amines that contain an array of Lewis acid and/or Lewis base-sensitive functional groups are rare. [3-4] This is mainly due to the paucity of catalyst systems that can cleave the otherwise unreactive amino C–H bonds while overcoming the undesirable acid–base complexation. To overcome this fundamental issue, previously reported amino C–H functionalization methods have typically been confined to structurally simple

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[3] For selected reviews on transformations of C(sp^3)–H bonds, see: (a) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439−2463. (b) Davies, H. M.; Manning, J. R. *Nature* **2008**, *451*, 417−424. (c) Baudoin, O. *Chem. Soc. Rev.* **2011** *40*, 4902−4911. (d) Haibach, M. C.; Seidel, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 5010−5036. (e) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74−100. (f) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053−1064. (g) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q; Yu, J.-Q. *Chem. Rev.* **2017**, *117*, 8754−8786. (h) Chu, J. C. K.; Rovis, T. *Angew. Chem., Int. Ed.* **2018***, 57*, 62−101. (i) Davies, H. M.; Liao, K. *Nat. Rev. Chem.* **2019**, 3, 347−360.

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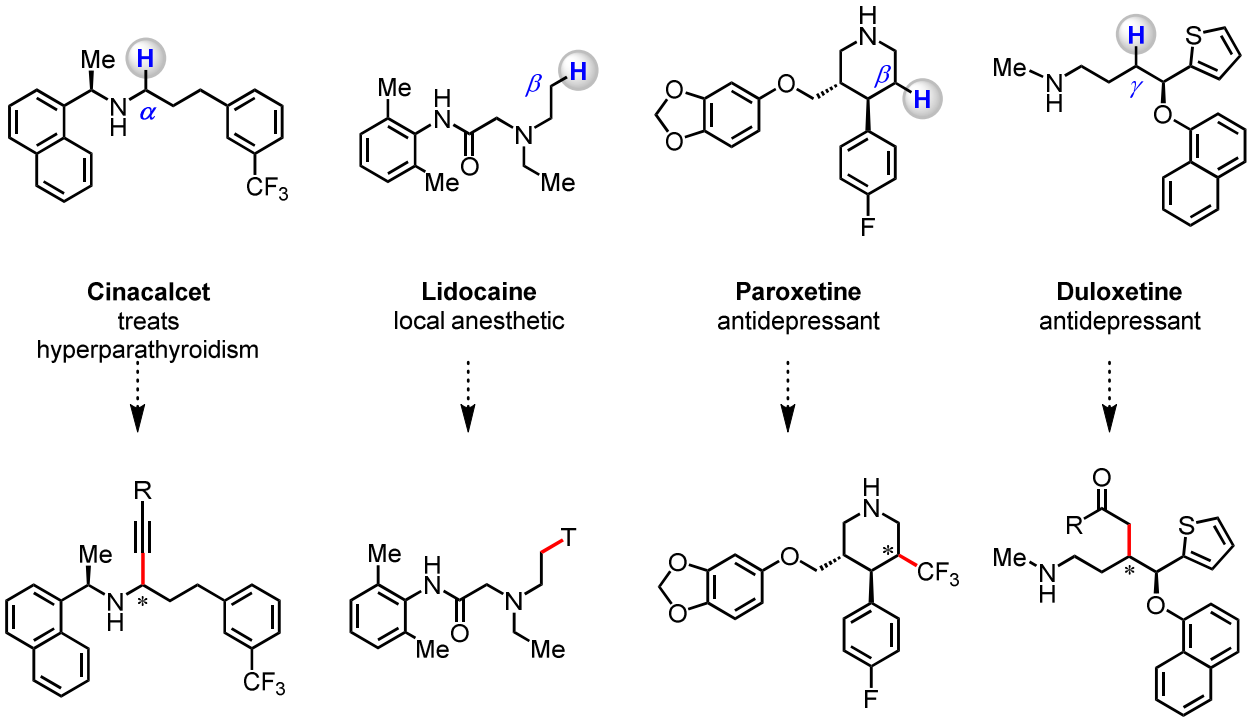
Scheme 3.1. Regioselective Amino C–H Functionalization of Bioactive Compounds



N-alkylamine substrates that have minimal steric and electronic affinities with the catalysts (see Schemes 3.2 and 3.3).

Homolytic or heterolytic cleavage of α-amino C–H bonds generate α-amino radical intermediates[5] or iminium ions[6] that are stabilized by hyperconjugation with the neighboring nitrogen atom and serve as versatile intermediates for achieving α-amino C–H functionalization.

[5] For advances in α-amino C–H functionalization via α-amino radical intermediates, see: (a) Noble, A.; MacMillan, D. W. *J. Am. Chem. Soc.* **2014**, *136*, 11602−11605. (b) Osberger, T. J.; Rogness, D. C.; Kohrt, J. T.; Stepan, A. F.; White, M. C. *Nature* **2016**, *537*, 214−219. (c) Le, C.; Liang, Y.; Evans, R. W.; Li, X.; MacMillan, D. W. C. *Nature* **2017**, *547*, 79−83. (d) McManus, J. B.; Onuska, N. P. R.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2018**, *140*, 9056−9060. (e) Ye, J.; Kalvet, I.; Schoenebeck, F.; Rovis, T. *Nat. Chem.* **2018**, *10*, 1037−1041.

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Transformations of α-amino C–H bonds can also be achieved through metal–carbenoid insertion,[7] and heteroatom-directed metalation (Scheme 3.2).[8-9] Conversion of γ-amino C–H bonds into C–C and C–heteroatom bonds has been performed by N-directed L_nPd-catalyzed cyclometalation (Scheme 3.3).[10] Despite these notable advances in α- and γ-amino C–H functionalizations, catalytic strategies to functionalize β-amino C–H bonds remain underdeveloped, particularly in an enantioselective manner. This is mainly due to the fact that radical or cationic intermediates generated by β-amino C–H activation are not readily accessible (vs. α-amino radical and iminium ions generated by α-amino C–H activation). Moreover, N-directed L_nPd-catalyzed β-amino C–H activation must proceed through the formation of strained four-membered palladacycle. Consequently, development of a broadly applicable catalyst system for regio- and enantio-selective transformations of β-amino C–H bonds that are applicable to late-stage functionalization of structurally complex bioactive amines represents a compelling research objective.

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[8] (a) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C. Y. *J. Am. Chem. Soc.* **2006**, *128*, 3538–3539. (b) Cordier, C. J.; Lundgren, R. J.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 10946–10949.
[9] Jain, P.; Verma, P.; Xia, G.; Yu, J. Q. *Nat. Chem.* **2017**, *9*, 140–144.
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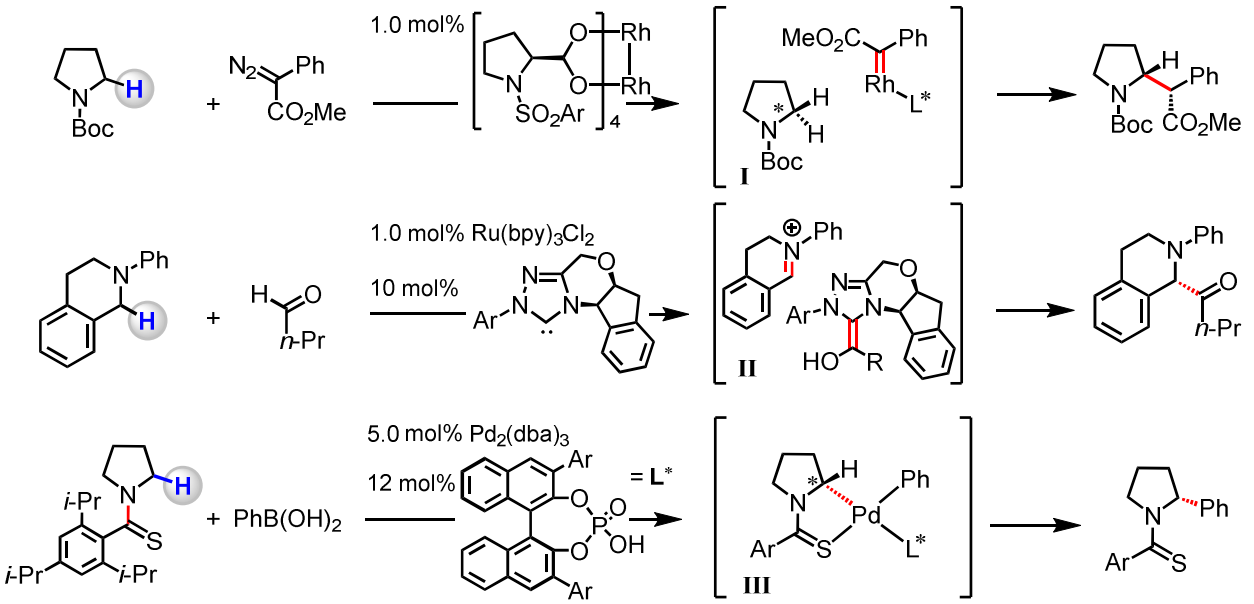
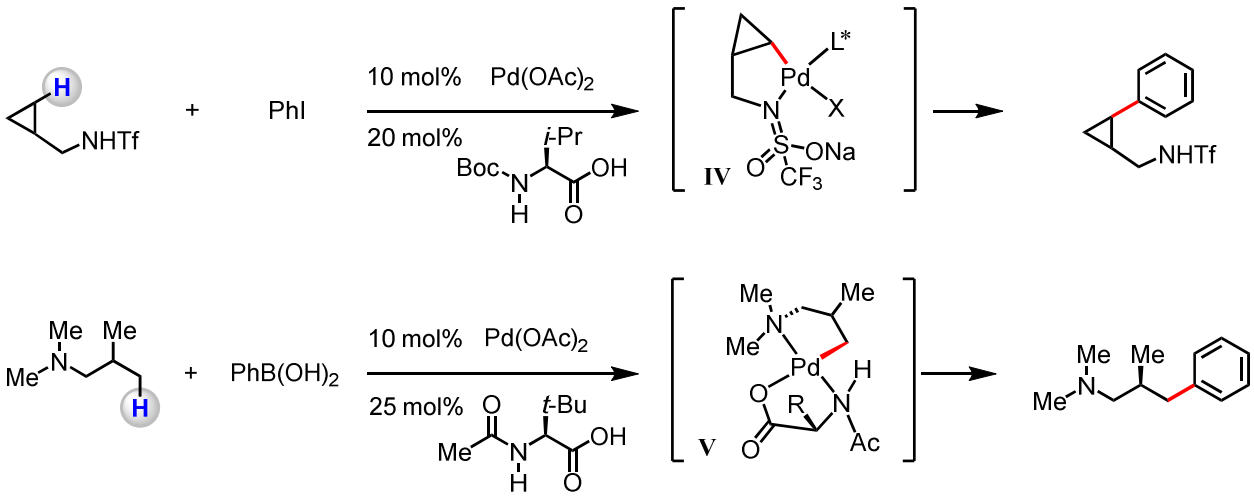
Scheme 3.2. Key Intermediates of Enantioselective α-Amino C–H Bond Functionalization



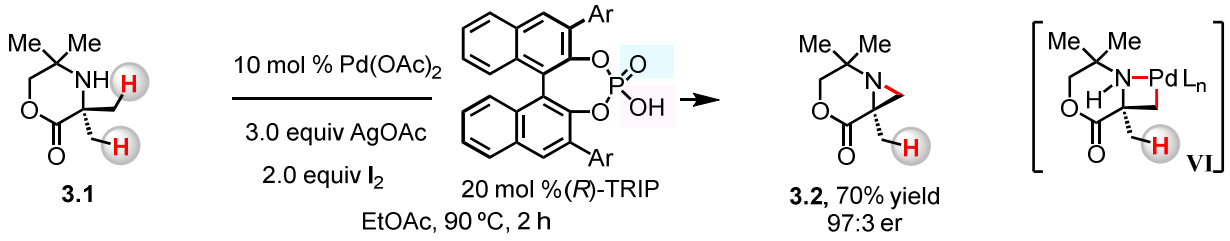
Scheme 3.3. Key Intermediates of Enantioselective γ-Amino C–H Bond Functionalization



3.1. Background

Despite the challenges associated with β-amino C–H functionalization, there are several reported methods for the synthesis of enantiomerically enriched β-substituted amines through activation of a β-amino C–H bond.[11] Gaunt and coworkers reported a Pd-catalyzed enantioselective C–H amination to afford aziridines using chiral phosphoric acid as an anionic ligand (Scheme 3.4).[11b] In the presence of 10 mol% $Pd(OAc)_2$, 20 mol% (*R*)-TRIP, and stoichiometric oxidant, the desired aziridine product **3.2** can be generated in 70% yield with 97:3 er through desymmetrization of *gem*-dimethyl groups in tetramethyl-morpholinone **3.1**. The authors proposed that (*R*)-TRIP/$Pd(OAc)_2$ complex could coordinate to the secondary amine of **3.1**, thereby allowing stereoselective C–H activation to take place to afford a four-membered cyclopalladation complex (**VI**). Although they have demonstrated they are able to achieve selective β-amino C–H activation, this method requires the sterically hindered amine substrates such as tetramethyl-morpholinone or piperazinone scaffold to overcome the undesired acid/base complexation. Furthermore, functional groups that readily react with AgOAc, I_2, and/or IOAc are problematic. Therefore, this method cannot be easily applied to the late stage functionalization of

Scheme 3.4. Palladium-Catalzyed Enantioselective C–H Activation of Aliphatic Amines

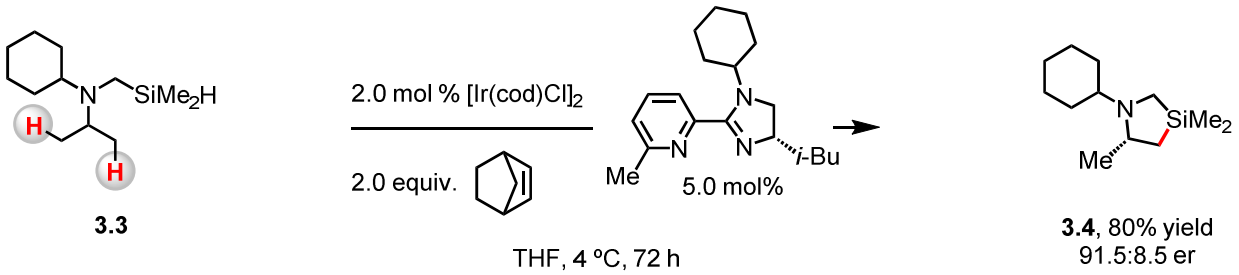


[11] (a) He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. *Science* **2014**, *343*, 1216–1220. (b) Smalley, A. P.; Cuthbertson, J. D.; Gaunt, M, J. *J. Am. Chem. Soc.* **2017**, *139*, 1412–1415. (c) Su, B.; Lee, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2018**, *140*, 18032–18038. (d) Lin, W.; Zhang, K.-F.; Baudoin, O. *Nat. Catal.* **2019**, *2*, 882–888.

N-containing drug molecules.

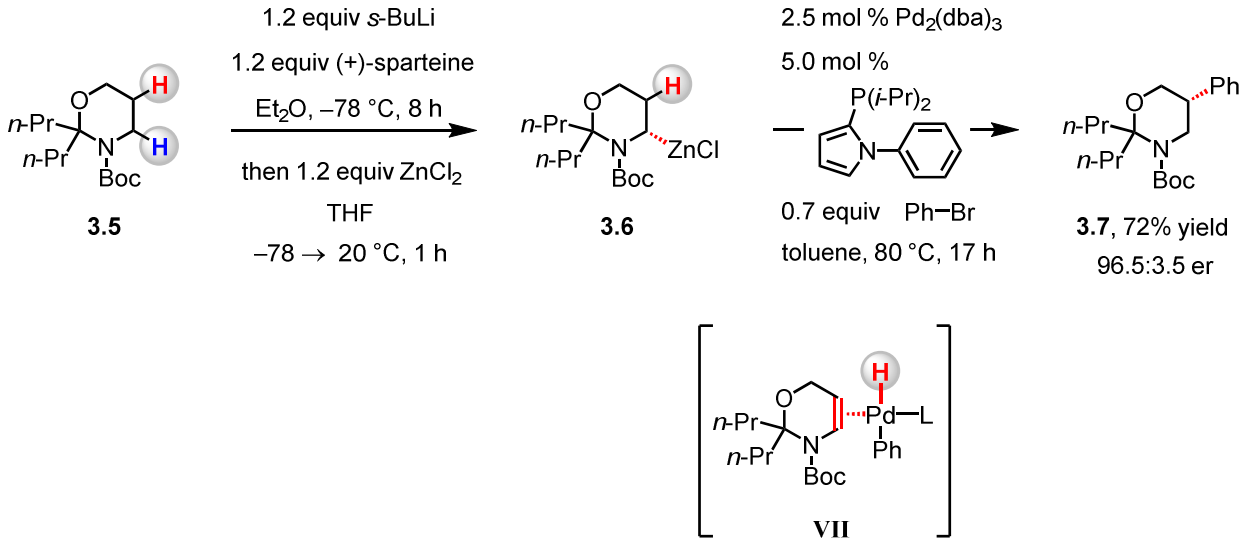
In 2018, Hartwig and coworkers developed a method for *β*-selective C(sp^3)–H silylation of aliphatic amine **3.3** to form silapyrrolidine **3.4** promoted by an Ir-based catalyst (Scheme 3.5).[11c] The reaction of (silylmethyl)amine **3.3** with 2.0 mol% Ir-based complex can generate silapyrrolidine **3.4** in 80% yield with 91.5:8.5 er. They proposed that the norbornene served as hydrogen acceptor for this transformation. However, this method requires the use of precious Ir-based catalyst and long reaction time. What's more, the use of silapyrrolidine substrate with Ir-based catalyst would be problematic with a wide variety of functional groups that may undergo reduction.

Scheme 3.5. Iridium-Catalzyed *β*-Selective C(sp^3)–H Silylation of Aliphatic Amines



In 2019, Baudoin and coworkers disclosed a regiodivergent enantioselective C–H functionalization of Boc-1,3-oxazinane **3.6** (Scheme 3.6).[11d] This one-pot reaction proceeds through sparteine-mediated enantioselective lithiation of Boc-1,3-oxazinane **3.5** to deliver an enantioenriched organozinc intermediate **3.6**. Without the isolation or purification of the organozinc species, Negishi coupling with phenyl bromide can give *β*-phenyl-substituted amine **3.7** in 72% yield in 96.5:3.5 er. However, the use of stoichiometric amounts of *s*-BuLi and (+)-sparteine could be problematic with various functional groups. Moreover, this enantioselective process can only be applied to Boc-1,3-oxazinanes.

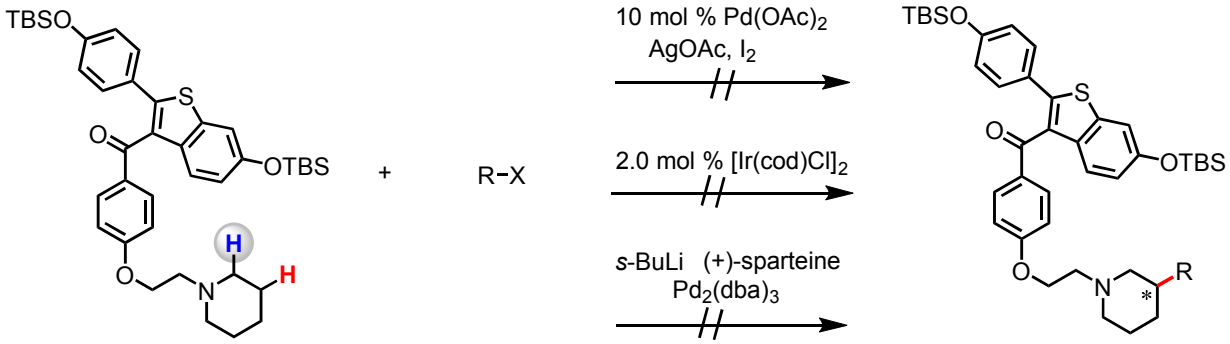
Scheme 3.6. Regiodivergent Enantioselective C–H Functionalization of Boc-1,3-oxazinanes



As the aforementioned literatures have shown, all three enantioselective methods demand the use of precious Ir- or Pd-based catalysts. In addition, strong oxidant (AgOAc, I_2, and/or IOAc) or base (*s*-BuLi) are also required which would be problematic with substrates that contain function groups that react with these reactive compounds. Consequently, these methods cannot be applied to the late stage functionalization of N-containing drug molecules that typically contain an array of acid, base and/or oxidant-sensitive functional groups (Scheme 3.7a). Considering the limitations of the state-of-the-art, we became intrigued in developing a sustainable element-based, highly functional group tolerant and enantioselective catalyst system that is applicable to the late stage *β*-amino C–H functionalization of N-containing drug molecules under redox-neutral conditions (Scheme 3.7b).

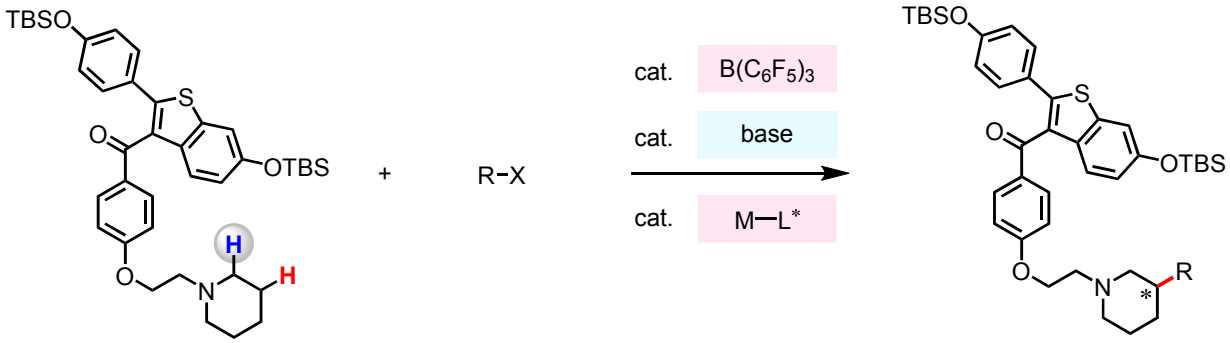
Scheme 3.7. Enantioselective *β*-amino C–H Functionalization

(a) Current Methods



limitations:
precious metal based catalyst
strong oxidant and strong base
poor function groups tolerance
not applicable to N-containing drug molecules

(b) Our Aim



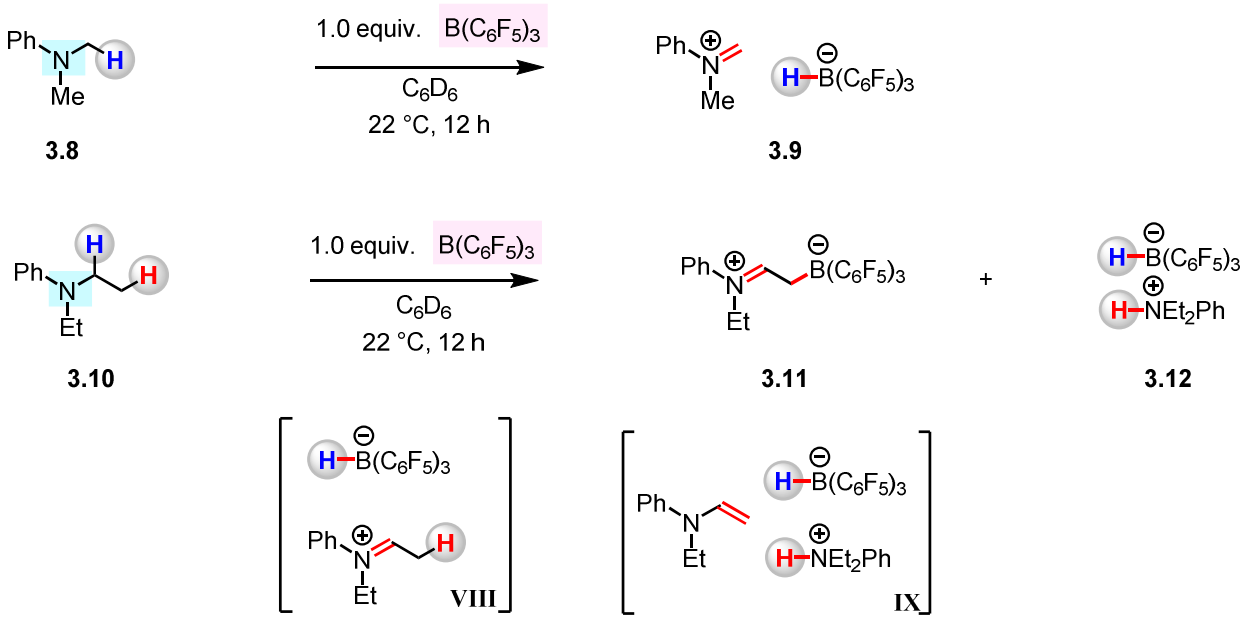
O-TBS raloxifene

Advantages:
nonprecious metal based catalyst
redox neutral
high function groups tolerance
applicable to N-containing drug molecules

3.2. Our Approach

Nonstereoselective *β*-amino C–H functionalization can be achieved through in situ generation of enamine from *N*-alkylamines.[12-13] In 2002, Santini and coworkers reported that $B(C_6F_5)_3$ could abstract hydride from the amine to give a borohydride/iminium complex (**3.8** → **3.9**) (Scheme 3.8).[12a] When diethyl aniline **3.10** were treated with $B(C_6F_5)_3$, ion pairs **3.11** and

Scheme 3.8. Reaction of $B(C_6F_5)_3$ and *N*-alkylamines



[12] For transformations that proceed through $(F_5C_6)_3B$-catalyzed hydride abstraction from *N*-alkylamines, see: (a) Millot, N.; Santini, C. C.; Fenet, B.; Basset, J. M. *Eur. J. Inorg. Chem.* **2002**, *2002*, 3328–3335. (b) Schwendemann, S.; Fröhlich, R.; Kehr, G.; Erker, G. *Chem. Sci.* **2011**, *2*, 1842–1849. (c) Maier, A. F. G.; Tussing, S.; Schneider, T.; Flörke, U.; Qu, Z.-W.; Grimme, S.; Paradies, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 12219–12223. (d) Kojima, M.; Kanai, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 12224–12227. (e) Maier, A. F. G.; Tussing, S.; Zhu, H.; Wicker, G.; Tzvetkova, P.; Flörke, U.; Daniliuc, C. G.; Grimme, S.; Paradies, J. *Chem. Eur. J.* **2018**, *24*, 16287–16291. (f) Zhang, J.; Park, S.; Chang, S. *J. Am. Chem. Soc.* **2018**, *140*, 13209–13213. (g) Chan, J. Z.; Chang, Y.; Wasa, M. *Org. Lett.* **2019**, *21*, 984–988. (h) Chang, Y.; Yesilcimen, A.; Cao, M.; Zhang, Y.; Zhang, B.; Chan, J. Z.; Wasa, M. *J. Am. Chem. Soc.* **2019**, *141*, 14570–14575. (h) Zhang, J.; Chang, S. *J. Am. Chem. Soc.* **2020**, *142*, 12585–12590.

[13] For *β*-amino C–H functionalization promoted by organometallic complexes through the formation of enamine intermediates, see: (a) Xia, X.-F.; Shu, X.-Z.; Ji, K.-G.; Yang, Y.-F.; Shaukat, A.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem*. **2010**, *75*, 2893–2902. (b) Sundararaju, B.; Tang, Z.; Achard, M.; Sharma, G. V. M.; Toupet, L.; Bruneau, C. *Adv. Synth. Catal*. **2010**, *352*, 3141–3146. (c) Sundararaju, B.; Achard, M.; Sharma, G. V. M.; Bruneau, C. *J. Am. Chem. Soc*. **2011**, *133*, 10340–10343. (d) Yuan, K.; Jiang, F.; Sahli, Z.; Achard, M.; Roisnel, T.; Bruneau, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 8876–8880.

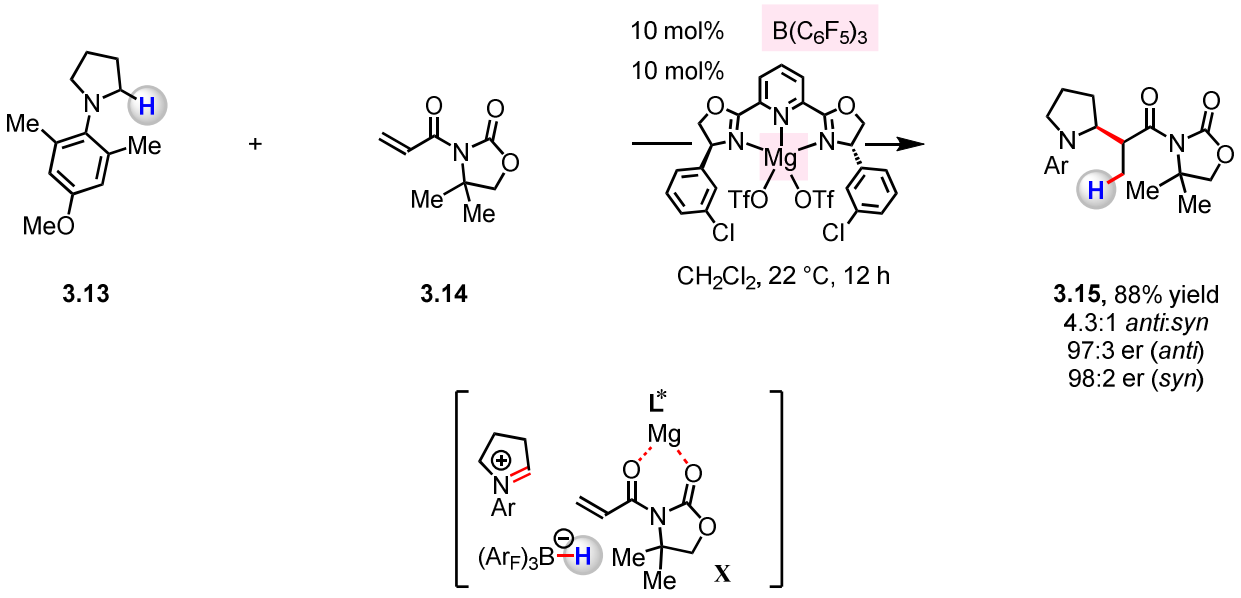
3.12 were observed by ^{1}H and ^{11}B NMR spectroscopy. They hypothesized that *N*-alkylamine **3.10** would undergo hydride abstraction to afford the intermediate **VIII**, which would then be deprotonated to yield an enamine intermediate **IX** consisting of a nucleophilic enamine and ion pair **3.12.** The nucleophilic enamine could attack the Lewis acid $B(C_6F_5)_3$ to give the complex **3.11**. This literature precedence has shown that sterically hindered $B(C_6F_5)_3$ could abstract hydride from *N*-alkylamines to generate electrophilic iminium ion. Further, when the *N*-alkylamines contain β-amino C–H, the iminium ion could undergo further deprotonation to give nucleophilic enamine intermediates.

Inspired by this pioneering work, our group have achieved enantioselective α-amino C–H functionalization through cooperative functions of $B(C_6F_5)_3$ and a chiral Lewis acid co-catalysts.[14] In 2018, we developed a method for enantioselective union of *N*-alkylamines **3.13** and α,β-unsaturated compounds **3.14** to produce β-amino carbonyl compounds **3.15** promoted by $B(C_6F_5)_3$ and a Mg-based catalyst (Scheme 3.9).[14a] For the catalytic enantioselective transformation, we have demonstrated sterically hindered $B(C_6F_5)_3$ could overcome mutual quenching with Lewis basic *N*-alkylamines and abstract hydride from a wide variety of *N*-alkylamines in a catalytic manner to generate iminium ion intermediate (**X**). The iminium ion intermediate can then react with in situ generated chiral Mg-enolate which is formed through boronhydride reduction to deliver the desired α-amino functionalized product **3.15** in 88% yield with up to 98:2 er.

Since we have shown that $B(C_6F_5)_3$ could abstract hydride in a catalytic manner, we then went to investigate whether $B(C_6F_5)_3$ and *N*-alkylamines could generate enamine intermediate in a

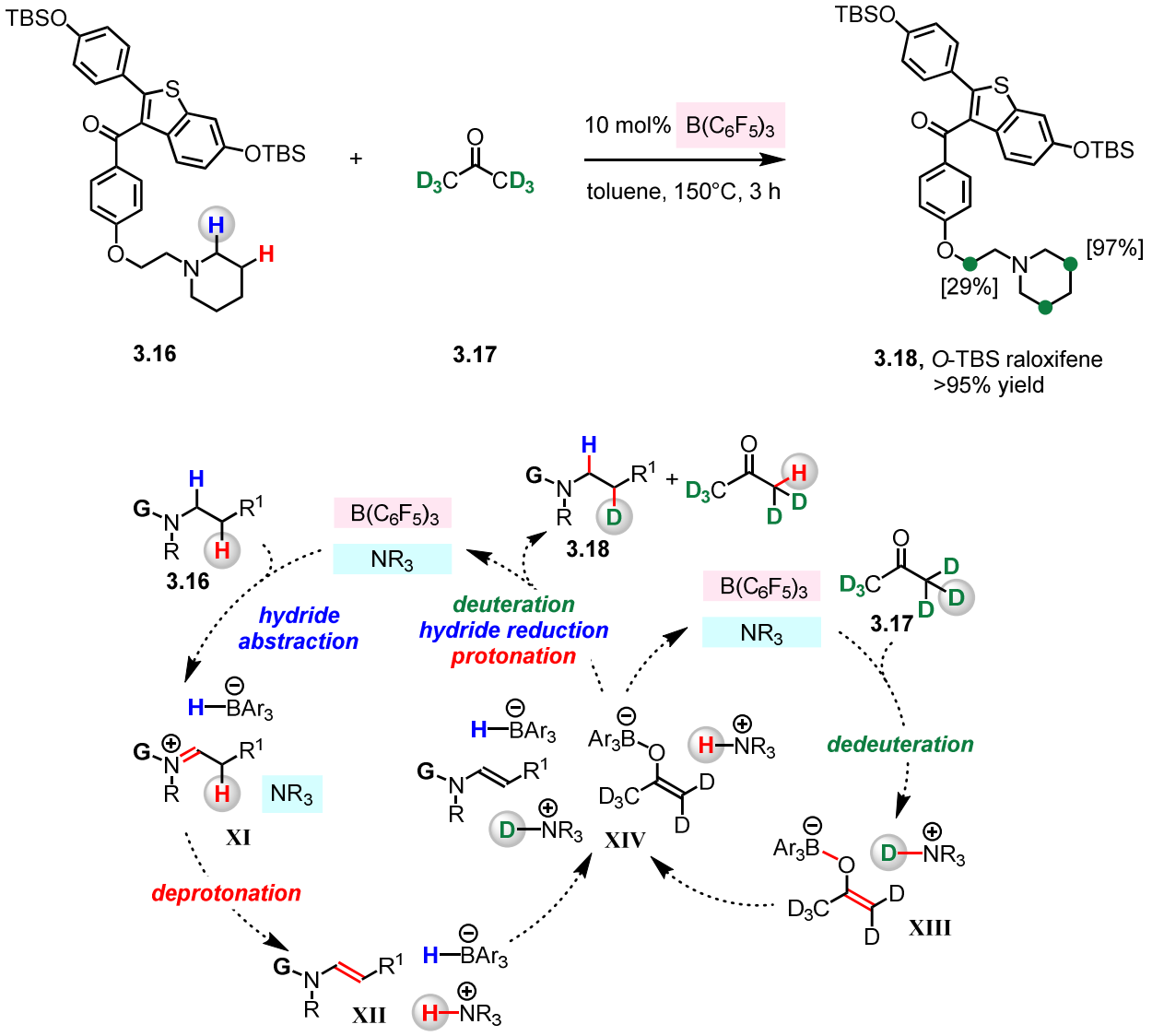
[14] (a) Shang, M.; Chan, J. Z.; Cao, M.; Chang, Y.; Wang, Q.; Cook, B.; Torker, S.; Wasa, M. *J. Am. Chem. Soc.* **2018**, *140*, 10593−10601. (b) Chan, J. Z.; Yesilcimen, A.; Cao, M.; Zhang, Y.; Zhang, B. C.; Wasa, M. *J. Am. Chem. Soc.* **2020**, *142*, 16493.

Scheme 3.9. Direct Enantioselective α-C–H Functionalization of Amines through Cooperative Action of $B(C_6F_5)_3$ and Chiral Mg-based Catalyst.



catalytic manner. In 2019, we disclosed a method for $B(C_6F_5)_3$-catalyzed hydrogen isotope exchange involving β-amino C–H bonds of various bioactive molecules (Scheme 3.10).[12h] Treatment of the *O*-TBS raloxifene **3.16** with only 10 mol% $B(C_6F_5)_3$ and acetone-d_6 **3.17** (6.8 equiv.), the desired product **3.18** can be obtained in >95% yield; 97% of cyclic β-amino C–H bonds were converted to C–D bonds while 27% of acyclic β-amino C–H bonds were converted to C–D bonds. We proposed that through the sequential hydride abstraction and deprotonation the enamine intermediate can be generated (**3.16** → **XI** → **XII**). At the same time, *N*-alkylamine could dedeuterate $B(C_6F_5)_3$-activated acetone-d_6 **3.17**, generating a boron enolate and a deuterated ammonium ion (**3.17** → **XIII**). Ensuing deuteration (**XIV**) of the enamine **XII** by **XIII** gives an iminium ion; subsequent borohydride reduction would afford β-deuterated product **3.18**. Here, we have developed a powerful catalyst system for selectively β-amino C–H deuteration of various important bioactive amine molecules.

Scheme 3.10. Catalytic Deuterium Incorporation within Metabolically Stable *β*-Amino C–H Bonds of Drug Molecules



The principles outlined herein, entailing conversion of amine containing drugs into nucleophilic enamine and its reaction with in situ generated electrophilic partner, provide a new rational framework for enantioselective *β*-amino C–H functionalization of bioactive amine molecules. In contemplating ways to develop a protocol for catalytic enantioselective *β*-amino C–H functionalization of *N*-alkylamines, we envisioned the use of a cooperative catalyst system

consisting of $B(C_6F_5)_3$, a Brønsted base catalyst, and a chiral Lewis acid co-catalyst (M–L*) (Scheme 3.11).[12,15-16] We proposed that $B(C_6F_5)_3$ could abstract hydride from *N*-alkylamine **3.19** to give a borohydride/iminium complex (**XV**). Then a Brønsted base catalyst would deprotonate **XV** to furnish enamine **XVI**. An stereoselective C–C bond formation between enamine **XVI** and the chiral Lewis acid co-catalyst activated α,β-unsaturated compound (**XVII**), would deliver zwitterionic **XVIII**. Ensuing protonation and reduction of **XVII** would produce β-alkylation product **3.21**.

The key advantage provided by the untethered and independently operational catalyst system is that both the efficiency and stereoselectivity can be easily optimized by evaluation of readily accessible Lewis acids, Brønsted base and chiral ligands. However, the fundamental challenge of cooperative catalyst system is that Lewis acidic and basic units among catalysts, substrates and products need to overcome mutual quenching. In addition, $B(C_6F_5)_3$ may have overlapping functions with the chiral Lewis acid co-catalyst (M–L*) for the activation of α,β-unsaturated compound, which would lead to racemic background reaction. Therefore, we need to develop potent cooperative catalyst system that can overcome these challenges and promote the catalytic enantioselective β-amino C–H functionalization of *N*-alkylamine.

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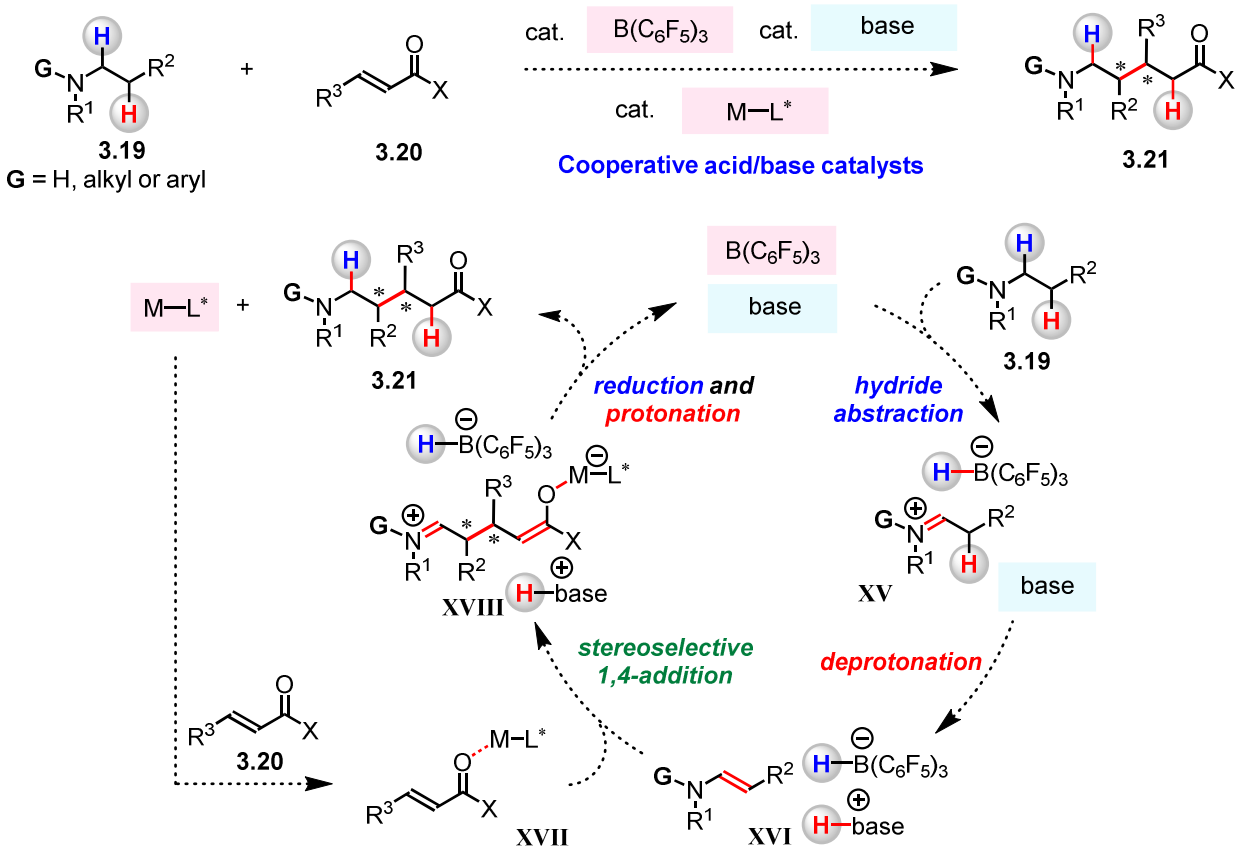
[15] (a) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603–614. (b) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534–561.

[16] For reviews on frustrated Lewis pair chemistry, see: (a) *Frustrated Lewis Pairs I: Uncovering and Understanding*; Stephan, D. W.; Erker, G. Eds.; Springer: Berlin, 2013; Vol. 332. (b) *Frustrated Lewis Pairs II: Expanding the Scope*; Erker, G.; Stephan, D. W. Eds.; Springer: Berlin, 2013; Vol. 334. (c) Ashley, A. E.; O'Hare, D. *Top. Curr. Chem.* **2013**, *334*, 191–218. (d) Feng, X.; Du, H. *Tetrahedron Lett.* **2014**, *55*, 6959–6964. (e) Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2015**, *54*, 6400–6441. (f) Stephan, D. W. *J. Am. Chem. Soc.* **2015**, *137*, 10018–10032. (g) Stephan, D. W. *Science* **2016**, *354*, aaf7229. (h) Stephan, D. W. *Chem* **2020**, *6*, 1520–1526.

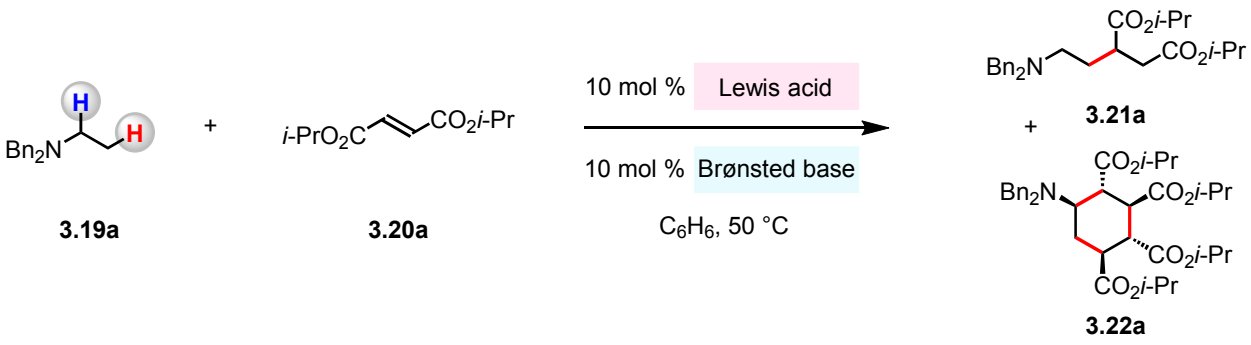
Scheme 3.11. Direct Enantioselective β-C–H Functionalization of Amines through Cooperative Actions of $B(C_6F_5)_3$ and Chiral Lewis Acid Co-catalyst.



3.3. Results and Discussion

To begin the investigation, we set out to study whether $B(C_6F_5)_3$ can activate both *N*,*N*-dibenzylethanamine (**3.19a**) and diisopropyl fumarate (**3.20a**), generating **3.21a** (Table 3.1). When we treated **3.19a** and **3.20a** with 10 mol% $B(C_6F_5)_3$ and various Brønsted base catalysts, the desired product **3.21a** can be obtained in up to 50% yield (entries 1–3). Other than the desired product **3.21a**, over alkylation product **3.22a** can be generated (entries 1–6), which probably was formed through the conjugated addition of a boron enolate (**XVIII**) to the **3.20a** followed by the intramolecular cyclization. Control experiments showed that in the absence of Brønsted base

Table 3.1. Evaluation of Lewis Acid Co-Catalyst



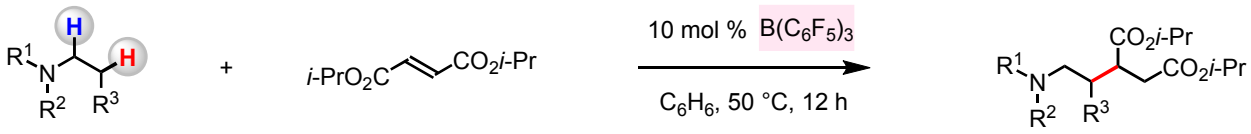
entry	Lewis acid	Brønsted base	time (h)	yield of **3.21a** (%)	yield of **3.22a** (%)
1	$B(C_6F_5)_3$	Et_3N	3	50	23
2	$B(C_6F_5)_3$	TMP	3	25	29
3	$B(C_6F_5)_3$	DBU	3	<5	<5
4	$B(C_6F_5)_3$	none	3	73	25
5[d]	$B(C_6F_5)_3$	none	3	54	5
6[d]	$B(C_6F_5)_3$	none	12	91	7
7	BCl_3	none	12	0	0
8	BPh_3	none	12	0	0
9	none	none	12	0	0

[a] Conditions: *N*,*N*-dibenzylethanamine (**3.19a**, 0.20 mmol), diisopropyl fumarate (**3.20a**, 0.30 mmol), Lewis acid, Brønsted base, C_6H_6 (0.20 mL), under N_2, 50 °C. [b] Yield was determined by the ^1H NMR analysis of unpurified reaction mixtures with *m*-xylene as the internal standard. [c] The structure and relative configuration of **3.22a** were established by the nuclear Overhauser effect spectroscopy (NOESY) studies. [d] 0.80 mL of C_6H_6 was used.

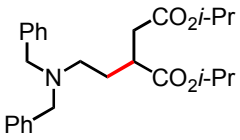
catalyst, the desired product **3.21a** can be obtained in 73% yield with over alkylation product **3.22a** in 25% yield. This implies that *N*-alkylamine substrate **3.19a**, product **3.21a** or **3.22a** can serve as the Brønsted base to deprotonate an iminium to deliver an enamine (**XV**→ **XVI**, Scheme 3.11). With more diluted reaction condition, the over alkylation product **3.22a** can be suppressed (entries 4–5). Further optimization leads us to obtain the desired product **3.21a** in 91% yield with 10 mol% $B(C_6F_5)_3$ in benzene for 12 hours (entry 6). Furthermore, without $B(C_6F_5)_3$ or with less hindered BCl_3 or less acidic BPh_3 as Lewis acid catalyst, the desired product cannot be obtained (entries 7–9). These results indicate that the potent sterically hindered Lewis acid $B(C_6F_5)_3$ with the sterically demanding and electron rich *N*-alkylamines represent the most effective combination for the β-amino C–H functionalization.

A variety of *N*-benzyl-substituted acyclic and cyclic amines may be used in the reaction with diisopropyl fumarate (**3.20a**) to generate the corresponding β-substituted amines (**3a**–**3f**, Table 3.2). Reaction with *N,N*-dibenzylethanamine **3.19a** and **3.20a** afforded **3.21a** in 88% yield. However, when *N,N*-dibenzylpropan-1-amine was used, product **3.21b** and **3.21c** can be generated in 58% and 33% yield, respectively. Compound **3.21c** is likely the result of intramolecular Mannich-type reaction between an iminium ion and enolate (**XVIII**, Scheme 3.11). With the more sizeable *N,N*-dibenzyl-2-methylpropan-1-amine, **3.21d** was obtained as the only product (69% yield), which is probably due to acceleration of the intramolecular cyclization by the Thorpe-Ingold effect. When cyclic amine, *N*-benzyl-4-(((*tert*-butyldimethylsilyl)oxy)methyl)piperidine **3.19d** was used, saturated product **3.21e** and enamine product **3.21f** can be generated in 74% and 26% yield, respectively. A series of aniline derived amines also reacted efficiently with **3.20a** to afford **3.21g**–**3.21j** (87–97% yield). When acyclic amine substrates were used, the desired product **3.21g** and **3.21h** can be obtained in 97% yield and 87% yield, respectively. The reaction with the

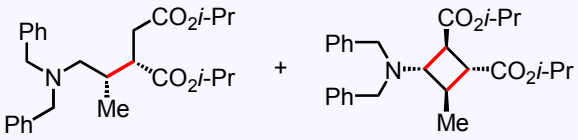
Table 3.2. *β*-Alkylation of Different *N*-Alkylamines



3.19 **3.20a** **3.21**

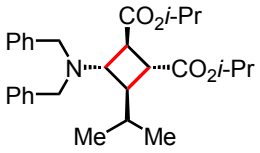


3.21a, 88% yield



3.21b, 58% yield[c]
1.3:1 dr

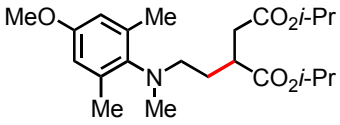
3.21c, 33% yield[c]
>20:1 dr



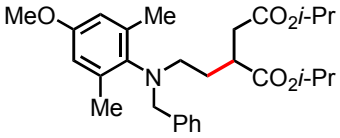
3.21d, 69% yield[d]
>20:1 dr

3.21e, 74% yield[c]
1.1:1 dr

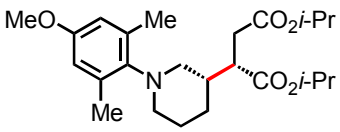
3.21f, 26% yield[c]
1.4:1 dr



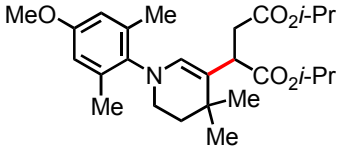
3.21g, 97% yield



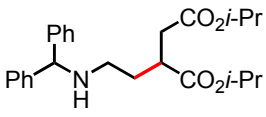
3.21h, 87% yield



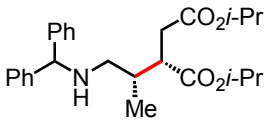
3.21i, 89% yield[c,e]
1.3:1 dr



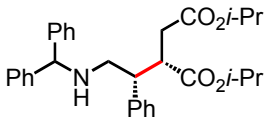
3.21j, 93% yield[f]



3.21k, 93% yield



3.21l, 66% yield[c]
1.1:1 dr



3.21m, 87% yield[c]
2.1:1 dr

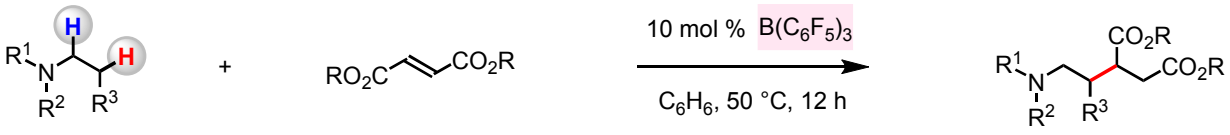
[a] Conditions: *N*-alkylamine (**3.19**, 0.20 mmol), diisopropyl fumarate (**3.20a**, 0.30–0.40 mmol), $B(C_6F_5)_3$ (10 mol %), C_6H_6, under N_2, 50 °C. [b] Yield of isolated and purified product. The dr values were determined by the ^1H NMR analysis of the unpurified reaction mixtures. [c] The structure and relative configuration of **3.21b** and **3.21e** were established by X-ray crystallographic analysis. The stereochemistry of **3.21f**, **3.21i**, **3.21l**, and **3.21m** were assigned in analogy. [d] The structure and relative configuration of **3.21d** were established by NOESY studies. The stereochemistry of **3.21c** was assigned in analogy. [e] 5.0 mol% of $B(C_6F_5)_3$ was used. [f] DCM was used as solvent. See section **3.7** for details.

cyclic amine **3.19g** furnished **3.21i** as the only product in 89% yield. However, with the more sterically hindered 4,4-dimethyl-substituted piperidine substrate **3.19h**, enamine **3.21j** was obtained in 93% yield. In addition, *N*-benzhydryl-substituted secondary amines **1.19i**, **1.19j** and **1.19k** were suitable substrates. The corresponding β-substituted amine products can be generated in up to 93% yield.

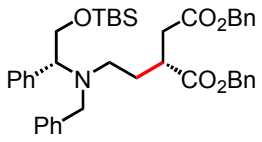
Next, we investigated reactions with different commercially available chiral *N*-alkylamines and drug molecules (Table 3.3). As a result, the employed chiral acyclic *N*-alkylamines gave product **3.21n** and **3.21o** in 69% yield (1.5:1 dr) and 90% yield (1.4:1 dr), respectively. In addition, these diastereomers are chromatographically separable, allowing us to obtain enantiomerically pure amino ester. Chiral pyrrolidines substrates can also be compatible. The protocol is also applicable to late-stage modification of N-containing drug molecules[17] that possess an array of Lewis acid-sensitive functional groups (**3.19p-3.19r**). In addition to the Lewis basic *N*-alkylamine moieties, a ketone, a benzothiophene, an ether, a pyrimidinone and a benzoisoxazole were tolerated. The reaction with *N*-benzyl paroxetine **3.19p** and **3.20a** afforded **3.21r** and **3.21s** in 39% and 14% yield, respectively. Silyl-protected raloxifene **3.19q** reacted efficiently with **3.20a** to afford **3.21t** in 80% yield and 2.5:1 dr. Risperidone **3.19r**, possessing more sterically hindered β-amino C–H bonds (vs. **3.19q**), was reacted with **3.20a**, furnishing enamine product **3.21u** (32% yield); minimal amounts (<5%) of the product derived from alkylation of acyclic β-amino C–H bond could be observed (^{1}H NMR analysis). For N-containing drug molecules such as paroxetine and raloxifene, although this method demands the installment of protecting groups in order to obtain high reactivity, the remove of those protecting groups can be easily achieved.

[17] Börgel, J.; Ritter, T. *Chem* **2020**, *6*, 1877–1887.

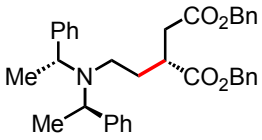
Table 3.3. Derivatization of Chiral Amines and Drugs



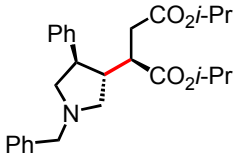
3.19 **3.20** **3.21**



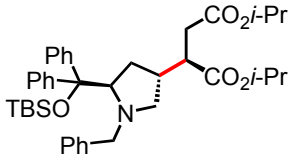
3.21n, 69% yield
(*R*,*R*):(*R*,*S*) = 1.5:1



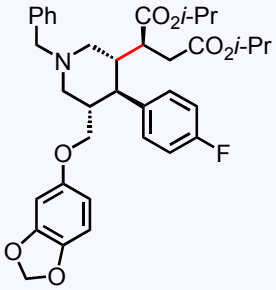
3.21o, 90% yield[d]
(*R*,*R*,*R*):(*R*,*R*,*S*) = 1.4:1

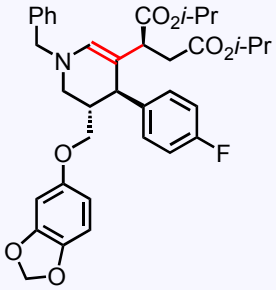


3.21p, 90% yield[e]
1.6:1 dr



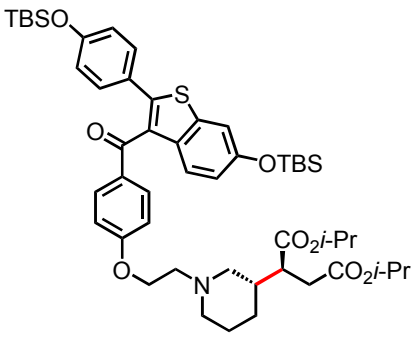
3.21q, 56% yield[e]
2.5:1 dr



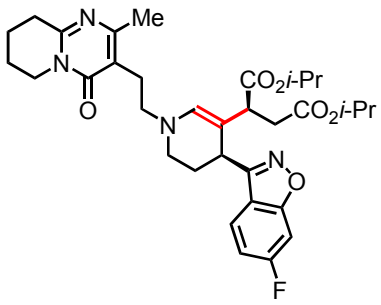


3.21r, **paroxetine derivative**[c]
39% yield, 2.3:1 dr

3.21s, **paroxetine derivative**[c]
14% yield, 1.9:1 dr



3.21t, **raloxifene derivative**[c]
80% yield, *anti*:*syn* = 1:2.5

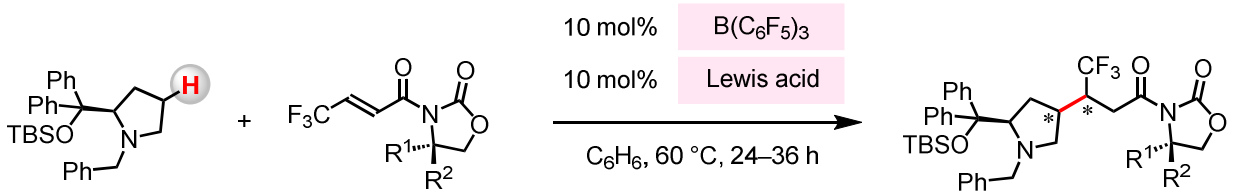


3.21u, **risperidone derivative**[c]
32% yield, 1.7:1 dr

[a] Conditions: *N*-alkylamine (**3.19**, 0.20 mmol), dialkyl fumarate (**3.20**, 0.30–0.40 mmol), $B(C_6F_5)_3$ (10 mol %), C_6H_6, under N_2, 50 °C. [b] Yield of isolated and purified product. The dr values were determined by the ^1H NMR analysis of the unpurified reaction mixtures. [c] The structure and relative configuration of **3.21t** and **3.21u** were assigned in analogy. The stereochemistry of **3.21r** and **3.21s** was assigned in analogy and also by the NOESY studies. [d] The absolute configuration of **3.21o** was determined based on the specific rotation of the derivative. [e] The structure and absolute configuration of **3.21q** was established by the X-ray crystallographic analysis. The stereochemistry of **3.21p** was assigned in analogy and also by the NOESY studies. See section **3.7** for details.

Although enantiomerically pure β-substituted amine product can be obtained, we can only obtain the desired product in up to 2.5:1 dr. We proposed through the use of enantiomerically pure electrophile, diastereoselectivity can be further improved. For the initial investigation, we choseto utilize the prolinol derivative **3.19o** and α,β-unsaturated oxazolidinone **3.23** as model substrate (Table 3.4). Indeed, with $B(C_6F_5)_3$ as the only catalyst, reaction with **3.19o** and (*S*,*E*)-4-phenyl-3 -(4,4,4-trifluorobut-2-enoyl)oxazolidin-2-one **3.23a** can deliver the desired product **3.24a** in 26% yield (7.0:1 dr, entry1). To further improve the reaction yield and diastereoselectivity, various representative Lewis acid co-catalysts were then evaluated, the latter of which may activate **3.23a**

Table 3.4. Optimization of Diastereoselective Reaction



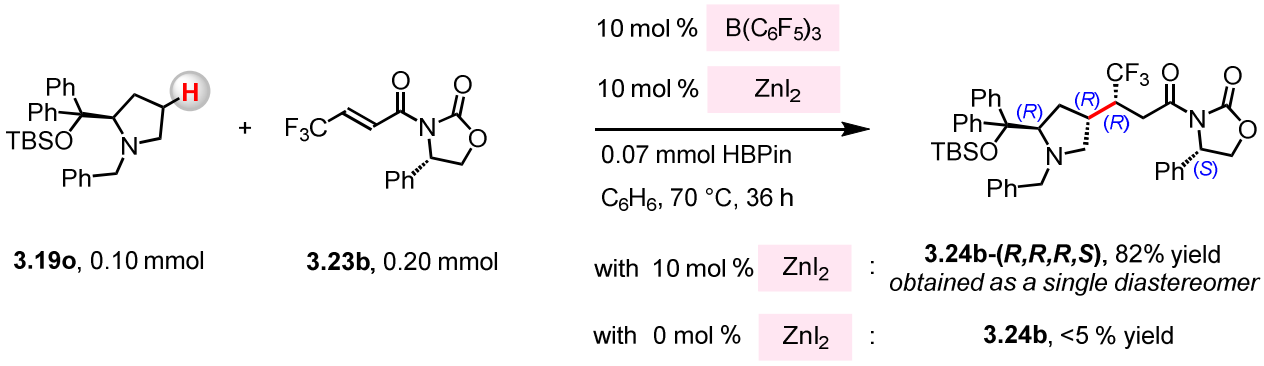
3.19o, 0.10 mmol **3.23**, 0.15 mmol **3.24**

entry	Lewis acid	R^1	R^2	time (h)	yield (%) and dr
1	none	H	Ph	24	26 7.0:1
2	$Mg(OTf)_2$	H	Ph	24	17 2.4:1
3	$Sc(OTf)_3$	H	Ph	24	30 1.0:1
4	$Zn(OTf)_2$	H	Ph	24	56 6.0:1
5	ZnI_2	H	Ph	24	64 8.0:1
6[b]	ZnI_2	H	Ph	24	56 18:1
7[b]	ZnI_2	Ph	H	24	65 >20:1
8[b,c]	ZnI_2	Ph	H	36	85 >20:1
9[b]	ZnI_2	H	H	36	25 7.0:1
10[b]	ZnI_2	H	Bn	36	24 7.0:1
11[b]	ZnI_2	H	*i*-Pr	36	35 6.0:1

[a]Conditions: (*R*)-1-benzyl-2-(((*tert*-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine (**3.19o**, 0.10 mmol), α,β-unsaturated compound (**3.23**, 0.15 mmol), $B(C_6F_5)_3$ (10 mol%), Lewis acid (10 mol%), C_6H_6 (0.60 mL), under N_2, 60 °C.[b] 70 mol% HBPin was added to the reaction mixture. [c]The reaction was performed at 70°C

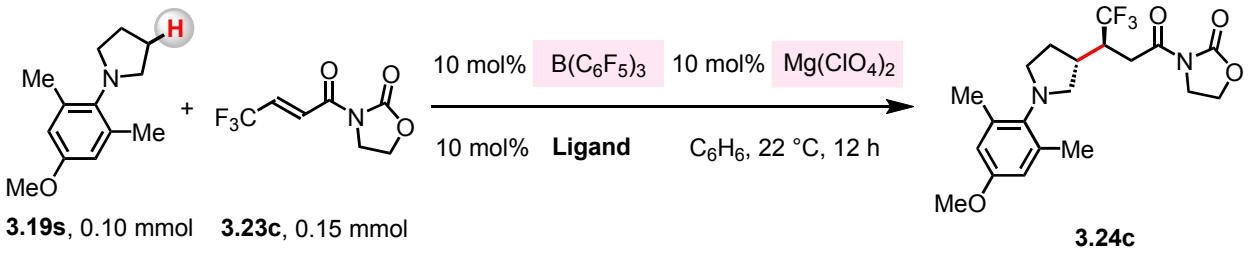
(entries 2–5); with 10 mol% ZnI_2 co-catalyst, the desired product **3.24a** can be obtained in 64% yield (8.0:1 dr). Furthermore, the addition of 70 mol% HBPin to the reaction was found to enhance the diastereoselectivity (18:1 dr, entry 6). When the opposite enantiomer (*S*,*E*)-4-phenyl-3-(4,4,4-trifluorobut-2-enoyl)oxazolidin-2-one **3.23b** was used, the desired product **3.24b** can be generated in 85% yield and as a single diastereomer (>20:1 dr, entries 7–8). Further optimization of the oxazolidinone structure does not lead to higher diastereoselectivity (entries 9–11). With 10 mol% $B(C_6F_5)_3$ and ZnI_2, **3.24b-(*R,R,R,S*)** can be isolated in 82% yield and as a single diastereomer (Scheme, 3.12).

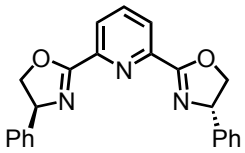
Scheme 3.12. Direct Diastereoselective β-C–H Functionalization of Chiral Amines through Cooperative Actions of $B(C_6F_5)_3$ and ZnI_2 Co-catalyst.



Having established this high diastereoselective process, we also explored the suitability of developing an enantioselective β-amino C–H alkylation reaction between achiral substrates **3.19s** and **3.23c**, promoted by a combination of $B(C_6F_5)_3$ and an enantiomerically pure organometallic co-catalyst (Table 3.5). We discovered that the combination of $Mg(ClO_4)_2$ and PhPybox (**L1**) or BnPybox (**L2**), afforded **3.24c** in 70% and 72% yield, and 82:18 and 85:15 er, respectively. With more sterically hindered **L3** and **L4**, the enantioselectivity cannot be further enhanced. However, when using the **L5** which contains longer alkyl chain, the enantioselectivity can be further improved to 90:10 er. With even longer alkyl chain **L6**, the enantioselectivity decreased to 80:20 er. What's more, with this substrate combination, neither efficiency nor the enantioselectivity could be improved by further catalyst optimization.

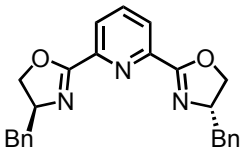
Table 3.5. Optimization Studies for Enantioselective β-Alkylation Involving **3.23c** with Chiral Mg-based Complexes





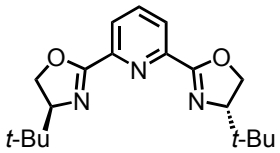
L1

3.24c, 70% yield
anti:*syn* =1.7:1
anti 82:18 er
syn 81:19 er



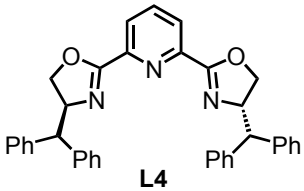
L2

3.24c, 72% yield
anti:*syn* =1.4:1
anti 85:15 er
syn 85:15 er



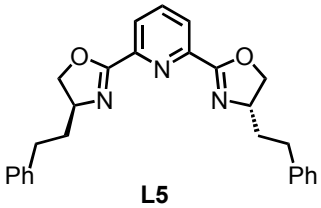
L3

3.24c, 30% yield
anti:*syn* =2.7:1
anti 30:70 er
syn 30:70 er



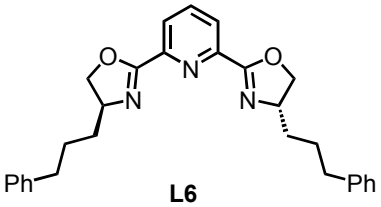
L4

3.24c, 30% yield
anti:*syn* =1.7:1
anti 53:47 er
syn 53:47 er



L5

3.24c, 67% yield
anti:*syn* =1.6:1
anti 90:10 er
syn 84:16 er



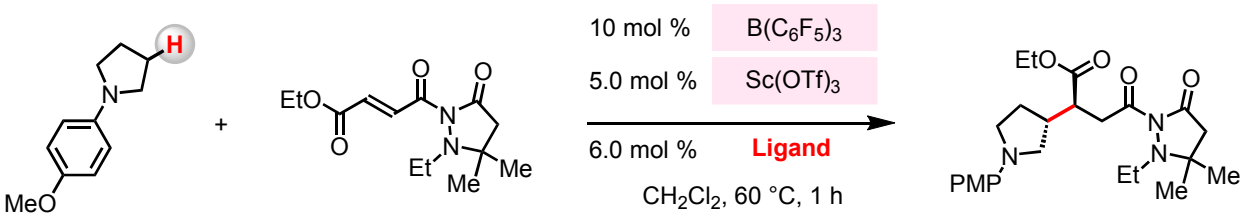
L6

3.24c, 75% yield
anti:*syn* =1.7:1
anti 80:20 er
syn 80:20 er

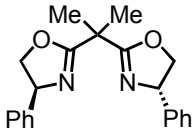
[a] Conditions: 1-(4-methoxy-2,6-dimethylphenyl)pyrrolidine (**3.19s**, 0.10 mmol), (*E*)-3-(4,4,4-trifluorobut-2-enoyl)oxazolidin-2-one (**3.23c**, 0.15 mmol), $B(C_6F_5)_3$ (10 mol%), $Mg(ClO_4)_2$ (10 mol%), ligand (11 mol%), C_6H_6 (0.6 mL), under N_2, 22 °C, 12 h. [b] Yield and dr were determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. The er values were determined by HPLC analysis of the purified product.

To improve enantioselectivity, we investigated the transformations involving a number of

Table 3.6. Evaluation of Chiral Ligands for Enantioselective *β*-Alkylation of Amines

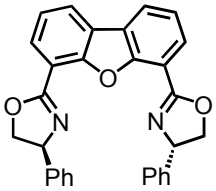


3.19t, 0.20 mmol **3.25a**, 0.30 mmol **3.26a**



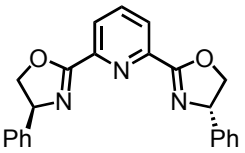
L7

3.26a, 57% yield
R*,*S*:*S*,*S = 2.0:1
R*,*S, 50:50 er
S*,*S, 50:50 er



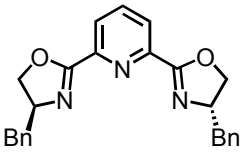
L8

3.26a, 46% yield
R*,*S*:*S*,*S = 2.0:1
R*,*S, 51:49 er
S*,*S, 50:50 er



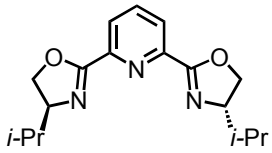
L1

3.26a, 72% yield
R*,*S*:*S*,*S = 5.0:1
R*,*S, 53:47 er
S*,*S, 58:42 er



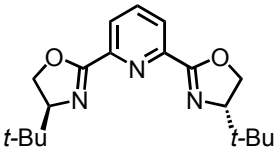
L2

3.26a, 60% yield
R*,*S*:*S*,*S = 2.0:1
R*,*S, 85:15 er
S*,*S, 80:20 er



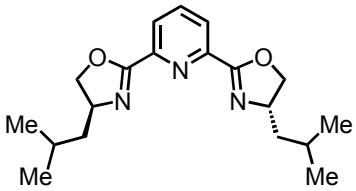
L9

3.26a, 80% yield
R*,*S*:*S*,*S = 4.0:1
R*,*S, 95:5 er
S*,*S, 94:6 er



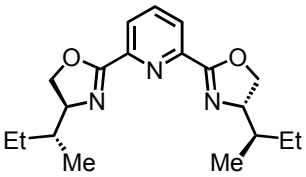
L3

3.26a, 85% yield
R*,*S*:*S*,*S = 1.7:1
R*,*S, 92:8 er
S*,*S, 93:7 er



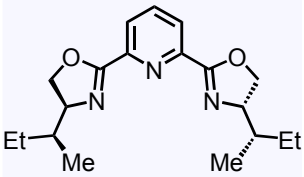
L10

3.26a, 72% yield
R*,*S*:*S*,*S = 2.7:1
R*,*S, 98:2 er
S*,*S, 98:2 er



L11

3.26a, 85% yield
R*,*S*:*S*,*S = 2.4:1
R*,*S, 92:8 er
S*,*S, 92:8 er



L12

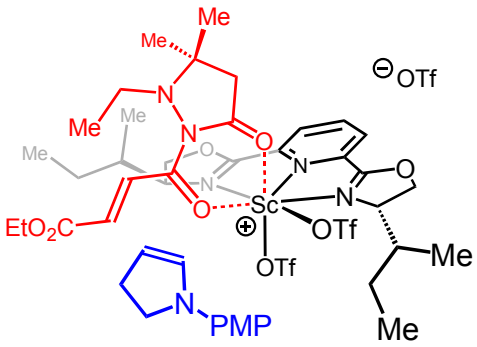
3.26a, 85% yield
R*,*S*:*S*,*S = 2.0:1
R*,*S, 97:3 er
S*,*S, 98:2 er

[a] Conditions: 1-(4-methoxyphenyl)pyrrolidine (**3.19t**, 0.20 mmol), ethyl (E)-4-(2-ethyl-3,3-dimethyl-5-oxopyrazolidin-1-yl)-4-oxobut-2-enoate (**3.25a**, 0.30 mmol), $B(C_6F_5)_3$ (10 mol%), $Sc(OTf)_3$ (5.0 mol%), ligand (6.0 mol%), CH_2Cl_2 (1.0 mL), under N_2, 60 °C, 1 h. [b] Yield and dr were determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. The er values were determined by HPLC analysis of the purified product.

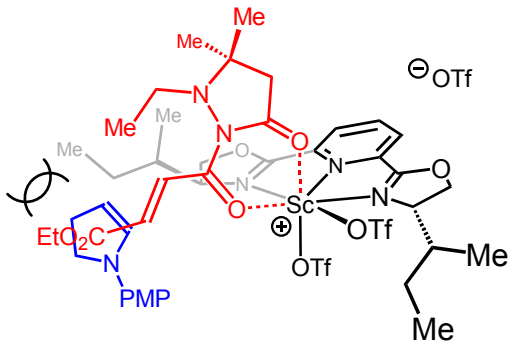
chiral Lewis acid co-catalysts and α,β-unsaturated compounds bearing different auxiliaries.[18] We found that 1-(4-methoxyphenyl)pyrrolidine **3.19t** reacts efficiently with 2-acryloylpyrazolidinone derivative **3.25a** in the presence of 10 mol % of $B(C_6F_5)_3$ together with $Sc(OTf)_3$ and various chiral bisoxazoline ligands (Table 3.6). We then found that reactions with Ph-substituted bisoxazoline ligand (e.g., **L1**, **L7**, **L8)** are hardly enantioselective (58:42–50:50 er). When the alkyl-substituted PyBOX ligands were employed (e.g., **L2**–**L3**, **L9**–**L10**), the enantioselectivity was enhanced and in the presence of (*S*)-*i*-Bu–PyBOX (**L10**), **3.26a** was formed in 72% yield, 2.7:1 dr and up to 98:2 er. Reaction efficiency can be further improved (85% yield) when **L11** and its diastereomer **L12** were used.

The stereochemical course of **3.19t**-derived enamine addition to [**L12**–$Sc(OTf)_3$]-activated **3.25a** can be rationalized by the models presented in Figure 3.1.[19] Models **XIX** and **XX** represent

Figure 3.1. Stereochemical Rationale for Enamine Addition to α,β-Unsaturated Compounds Catalyzed by **[L12**–$Sc(OTf)_3$**]**



XIX, favored



XX, disfavored

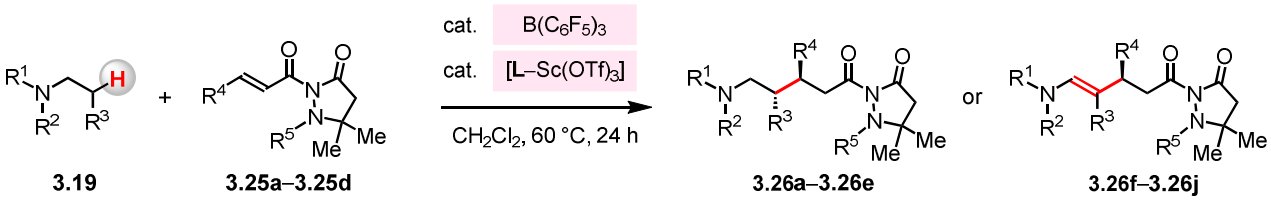
[18] (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256. (b) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800–3801. (c) Adachi, S.; Takeda, N.; Sibi, M. P. *Org. Lett.* **2014**, *16*, 6440–6443. (d) Espelt, L. R.; McPherson, I. S.; Wiensch, E. M.; Yoon, T. P. *J. Am. Chem. Soc.* **2015**, *137*, 2452–2455.

[19] (a) Evans, D. A.; Masse, C. E.; Wu, J. *Org. Lett.* **2002**, *4*, 3375–3378. (b) Evans, D. A.; Fandrick, K. R.; Song, H-J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029–10041. (c) Sibi, M. P.; Itoh, K.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 5366–5367.

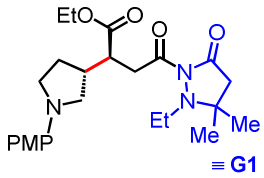
the energetically minimized structures of [**L12**–$Sc(OTf)_3$] docked with **3.25a**, respectively. As shown in model **XIX**, the high level of enantioselectivity observed in the formation of **3.26a-(*R*,*S*)** can be explained by selective 1,4-addition of the enamine to the *re*-face of [**L12**–$Sc(OTf)_3$]-bound **3.25a**; as depicted in model **XX**, the *si*-face is effectively shielded by a *sec*-butyl group of the PyBOX ligand.

Enantioselective reactions between an array of *N*-alkylamines and α,β-unsaturated compounds were carried out in the presence of $B(C_6F_5)_3$ and a **L**–$Sc(OTf)_3$ complex (Table 3.7). Various α,β-unsaturated compounds (**3.25a–3.25d**) bearing ester, ketone, or CF_3 groups can react with 1-(4-methoxyphenyl)pyrrolidine (**3.19t**) to afford the β-functionalized product in 62–83% yield, 2.0:1–6.7:1 dr and 95:5–98:2 er. The reaction of **3.19t** with **3.25a** (R^5 = Et) and **3.25b** (R^5 = Bn) gave **3.26a** (2.0:1 dr, up to 98:2 er) and **3.26b** (3.0:1, up to 95:5 er), respectively. These results indicate that *N*-substituents of the pyrazolidinone unit could have influence over both diastereo- and enantioselectivity. The reaction between acyclic *N*-ethyl-4-methoxy-*N*,2,6-trimethylaniline **3.19e** and **3.25d** would deliver the *N*-arylpiperidine derivative **3.26e** in 67% yield (>20:1 dr, 95:5 er) (Scheme 3.13a). We proposed that the generation of **3.26e** probably entails β-amino C–H alkylation of **3.19e** by **3.25d** to afford a zwitterionic intermediate containing an iminium and an enolate (**XXI**), followed by isomerization of the iminium to give **XXI**; then intramolecular cyclization between the iminium and the enolate gives **3.26e**. Furthermore, various *N*-aryl substituted cyclic amines (**3.19g-3.19h**, **3.19u**) were found to be compatible with this enantioselective β-alkylation to generate enamines **3.26f–3.26h** in 74–95% yield and 94:6–96:4 er. The reaction of *N*-arylpiperidine-3,3,5,5-d_4 **3.19g-*d*** (0.10 mmol) and **3.25d** (0.20 mmol) delivered **3.26f-*d*** (84% yield, 95:5 er) and **3.27d-*d*** (0.08 mmol; Scheme 3.13b). Spectroscopic analysis of

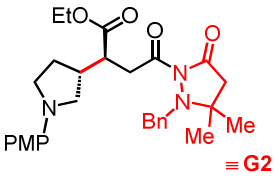
Table 3.7. Evaluation of Chiral Ligands for Enantioselective β-Alkylation of Amines



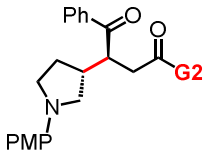
3.19 **3.25a–3.25d** **3.26a–3.26e** **3.26f–3.26j**



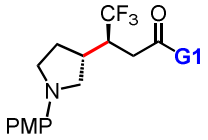
3.26a, 80% yield
(*R*,*S*):(*S*,*S*) = 2.0:1
(*R*,*S*) 97:3 er
(*S*,*S*) 98:2 er



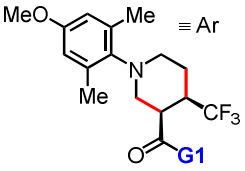
3.26b, 83% yield[b]
(*R*,*S*):(*S*,*S*) = 3.0:1
(*R*,*S*) 95:5 er
(*S*,*S*) 95:5 er



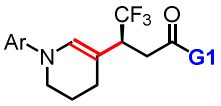
3.26c, 78% yield[b]
(*R*,*S*):(*S*,*S*) = 3.5:1
(*R*,*S*) 95:5 er
(*S*,*S*) 95:5 er



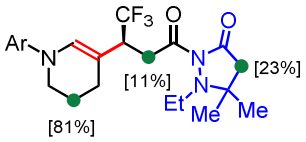
3.26d, 62% yield
(*R*,*S*):(*S*,*S*) = 6.7:1
(*R*,*S*) 96:4 er
(*S*,*S*) 95:5 er



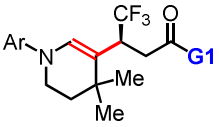
3.26e, 67% yield[c,d]
(*R*,*R*):(*S*,*R*) = >20:1
(*R*,*R*) 95:5 er



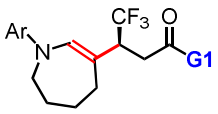
3.26f, 95% yield
95:5 er



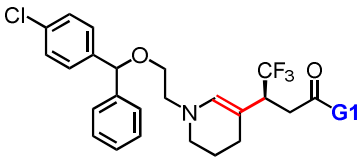
3.26f-*d*, 84% yield
95:5 er



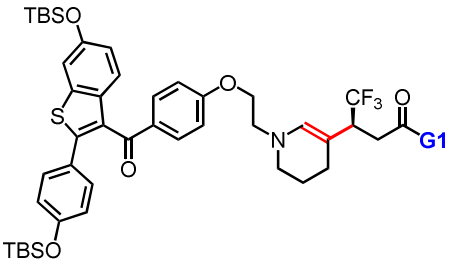
3.26g, 74% yield[e]
94:6 er



3.26h, 78% yield
96:4 er



3.26i, cloperastine derivative
53% yield
1.0:1 dr, 90:10 er[c,e,f]



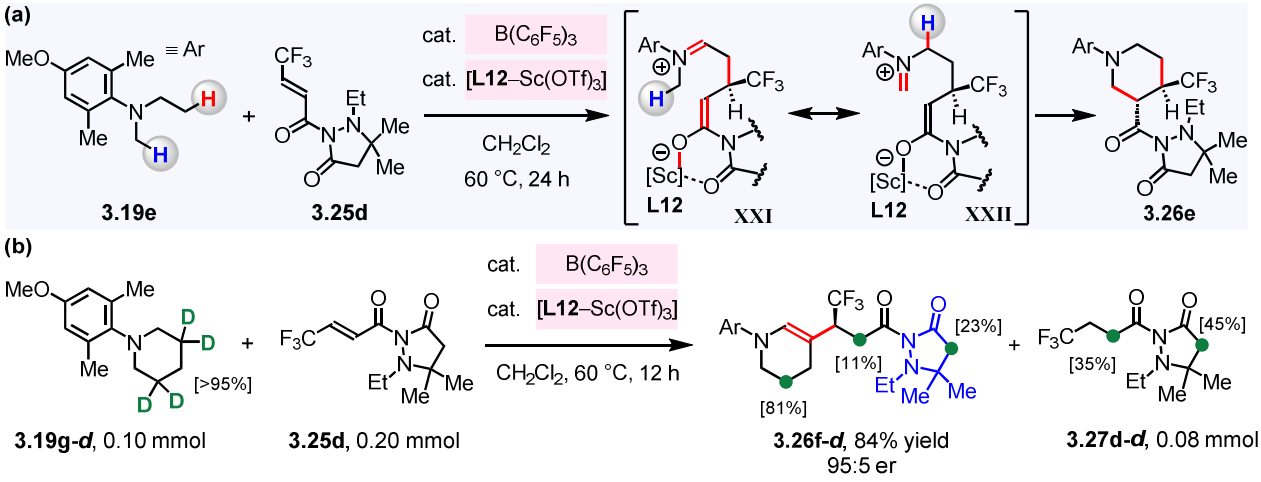
3.26j, raloxifene derivative
57% yield
95:5 er[c,e,f]

[a] Conditions: *N*-alkylamine (**3.19**, 0.10 mmol), α,β-unsaturated compound (**3.25**, 0.15–0.20 mmol), $B(C_6F_5)_3$ (10 mol%), **L12**–$Sc(OTf)_3$ (10 mol%), CH_2Cl_2 (1.0 mL), under N_2, 60 °C, 1–36 h. [b] 10 mol % of **L9**–$Sc(OTf)_3$ was used. [c] 20 mol % of $B(C_6F_5)_3$ was used. [d] 20 mol % of **L12**–$Sc(OTf)_3$ was used. [e] The reaction was performed at 80 °C. [f] 10 mol % of **L10**–Sc(OTf)3 was used. See section **3.7** for details.

3.26f-*d* and **3.27d-*d*** revealed that there is deuterium incorporation at their enolizable α-carbonyl units, and that there is D/H exchange at C5 of **3.26f-*d*** (>95% in **3.19g-*d*** → 81% in **3.26f-*d***).[12h] These results imply that in situ generated $[(F_5C_6)_3B–H]^-$ $[base–D]^+$ reacts with **3.25d** to produce

3.27d-*d* to regenerate $B(C_6F_5)_3$ (vs by releasing H–D). We were able to employ this method for the *β*-C–H functionalization of bioactive trialkylamines, including cloperastine (cough suppressant) **3.19v** and raloxifene (estrogen modulator) **3.19q**, to generate enamines **3.26i** and **3.26j** in 53% yield (90:10 er) and 57% yield (95:5 er), respectively.

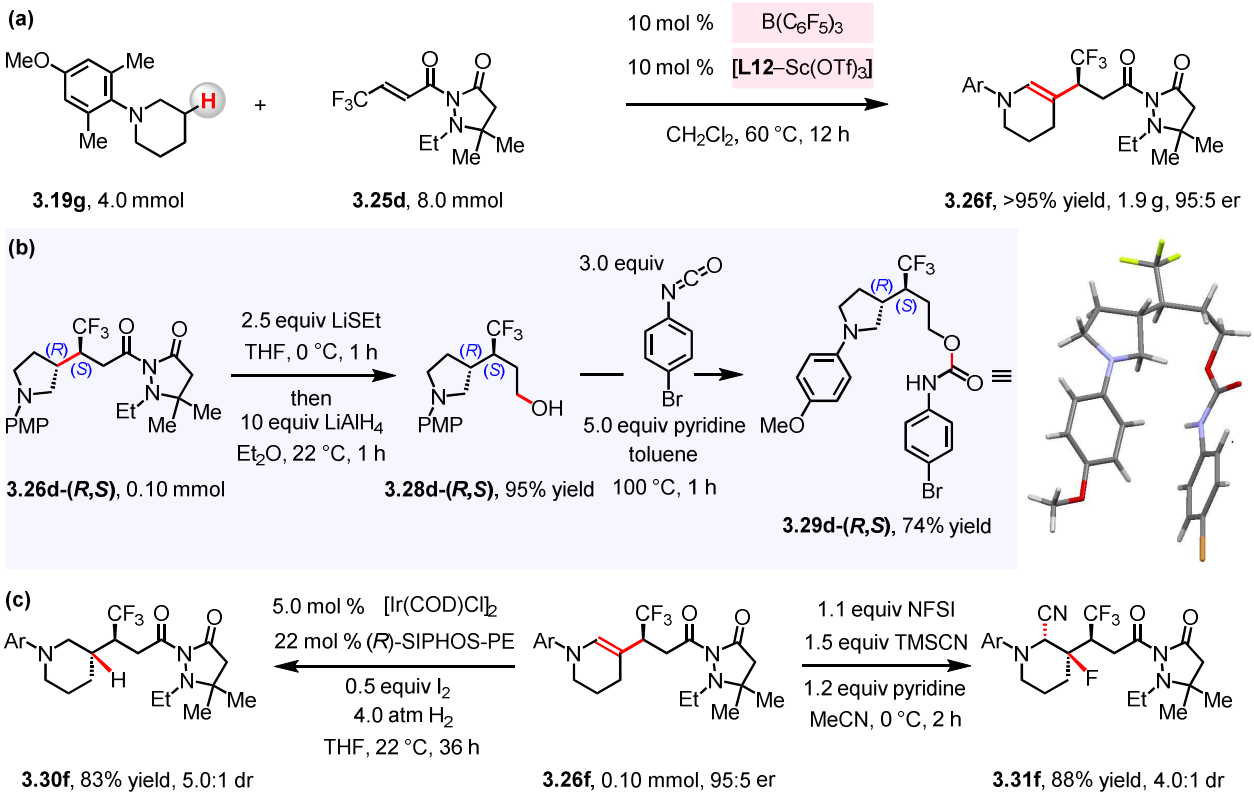
Scheme 3.13. Additional Data Interpretation



The catalytic method is scalable. Treatment of 4.0 mmol of *N*-arylpiperidine **3.19g** and **3.25d** with 10 mol % $B(C_6F_5)_3$, and 10 mol % **L12**–$Sc(OTf)_3$, (CH_2Cl_2, 12 h, 60 °C) generated **3.26f** in 95% yield (1.9 g; Scheme 3.14a). Treatment of **3.26d-(*R,S*)** with LiSEt followed by reduction of the resulting thioester with $LiAlH_4$ afforded alcohol **3.28d-(*R,S*)** in 95% overall yield (Scheme 3.14b). Compound **3.28d-(*R,S*)** was subsequently converted to its derived carbamate **3.29d-(*R,S*)** which was subjected to the X-ray crystallographic analysis for determination of absolute configuration (see the Supporting Information for details). Enamines obtained by enantioselective *β*-alkylation were found to be versatile intermediates (Scheme 3.14c). Hydrogenation of enamine **3.26f** by a chiral Ir-based catalyst afforded **3.30f** in 83% yield and 5.0:1

dr,[20a] and treatment of **3.26f** with NFSI and TMSCN gave fluorocyanation product **3.31f** in 88% yield and 4.0:1 dr.[20b]

Scheme 3.14. Modification of Products and Scalability



[20] (a) Hou, G. H.; Xie, J. H.; Yan, P. C.; Zhou, Q. L. *J. Am. Chem. Soc.* **2009**, *131*, 1366–1367. (b) Dilman, A. D.; Belyakov, P. A.; Struchkova, M. I.; Arkhipov, D. E.; Korlyukov, A. A.; Tartakovsky, V. A. *J. Org. Chem*, **2010**, *75*, 5367–5370.

3.4. Mechanistic Investigations

To gain insight regarding the mechanistic nuances of the catalytic process, we designed and performed mechanistic studies. These studies included determining reaction orders, kinetic isotope effects, and Hammett ρ values (Figure 3.2, Schemes 3.15 and 3.18, respectively). Additionally, these investigations led to revised pathways for catalytic β-C–H alkylation reaction (Schemes 3.16–3.17).

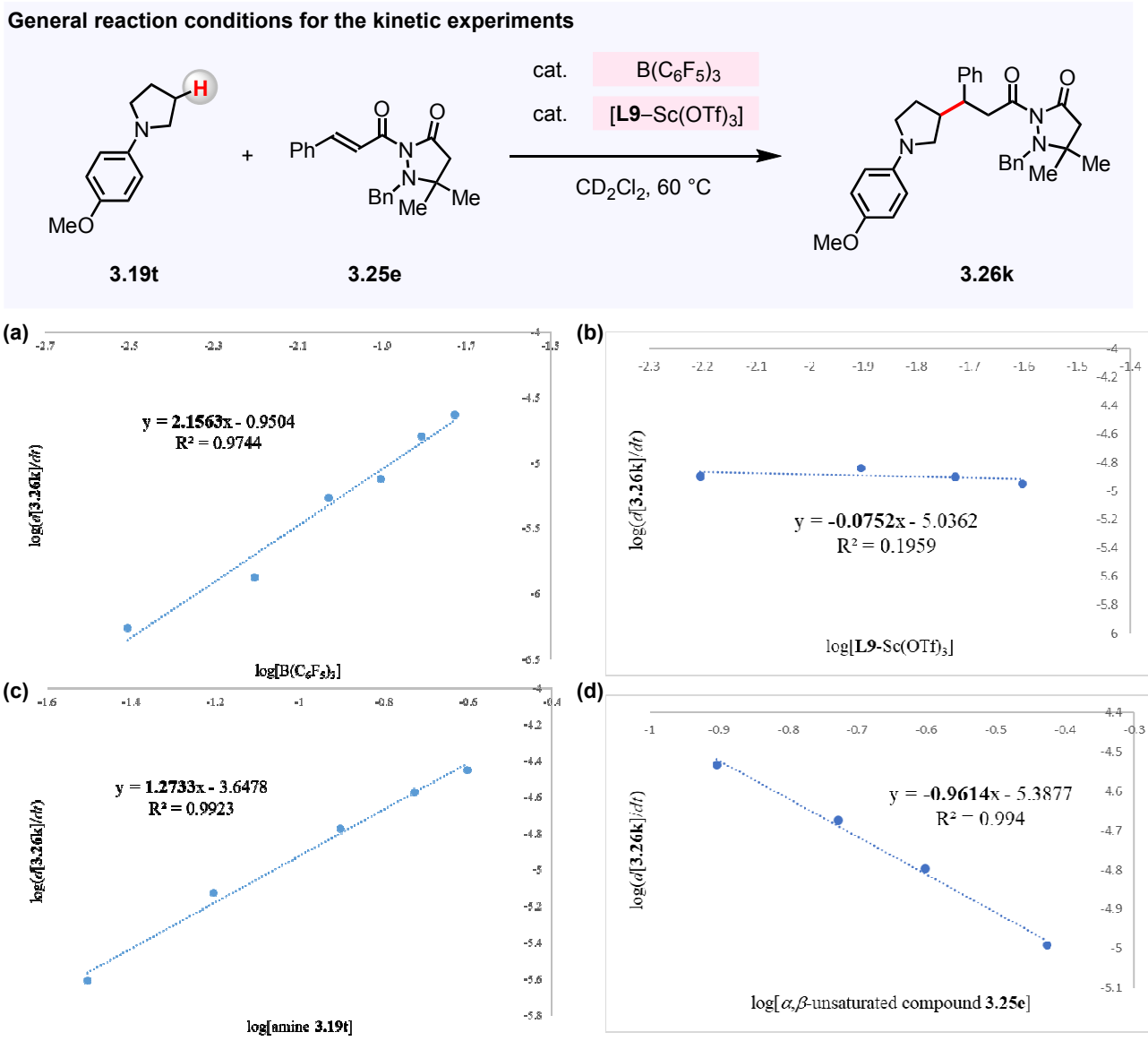
We first performed the kinetic experiments for the reaction of *N*-arylpyrrolidine **3.19t** with α,β-unsaturated compound **3.25e** to determine the order of each component of this reaction. The kinetic experiments suggest the following rate equation: second-order dependence on $B(C_6F_5)_3$ concentration (Figure 3.2a), zero order dependence on the concentration of **L9**–$Sc(OTf)_3$ complex (Figure 3.2b), first-order dependence on amine concentration of **3.19t** (Figure 3.2c), and reverse first-order dependence on the concentration of electrophile **3.25e** (Figure 3.2d). The independence of the reaction rate on the initial concentration of **L9**–$Sc(OTf)_3$ suggests that enantioselective C–C bond forming event between in situ generated enamine and [**L9**–$Sc(OTf)_3$]-activated **3.25e** (Scheme 3.11, **XVI** → **XVIII**) occurs after the turnover-limiting step. Additionally, this suggests that either the hydride abstraction step (**3.19** → **XV**) or the deprotonation step (**XV** → **XVI**) is likely the turnover-limiting step.

In order to figure out whether hydride abstraction step or the deprotonation step is the turnover-limiting step, we designed and performed independent kinetic isotope effect experiments to see whether α-C–H or β-C–H bond cleavage is involved in the turnover-limiting step.[21] However, independent rate measurements involving **3.19t** and **3.19t*α-d*** (Scheme 3.15a) were

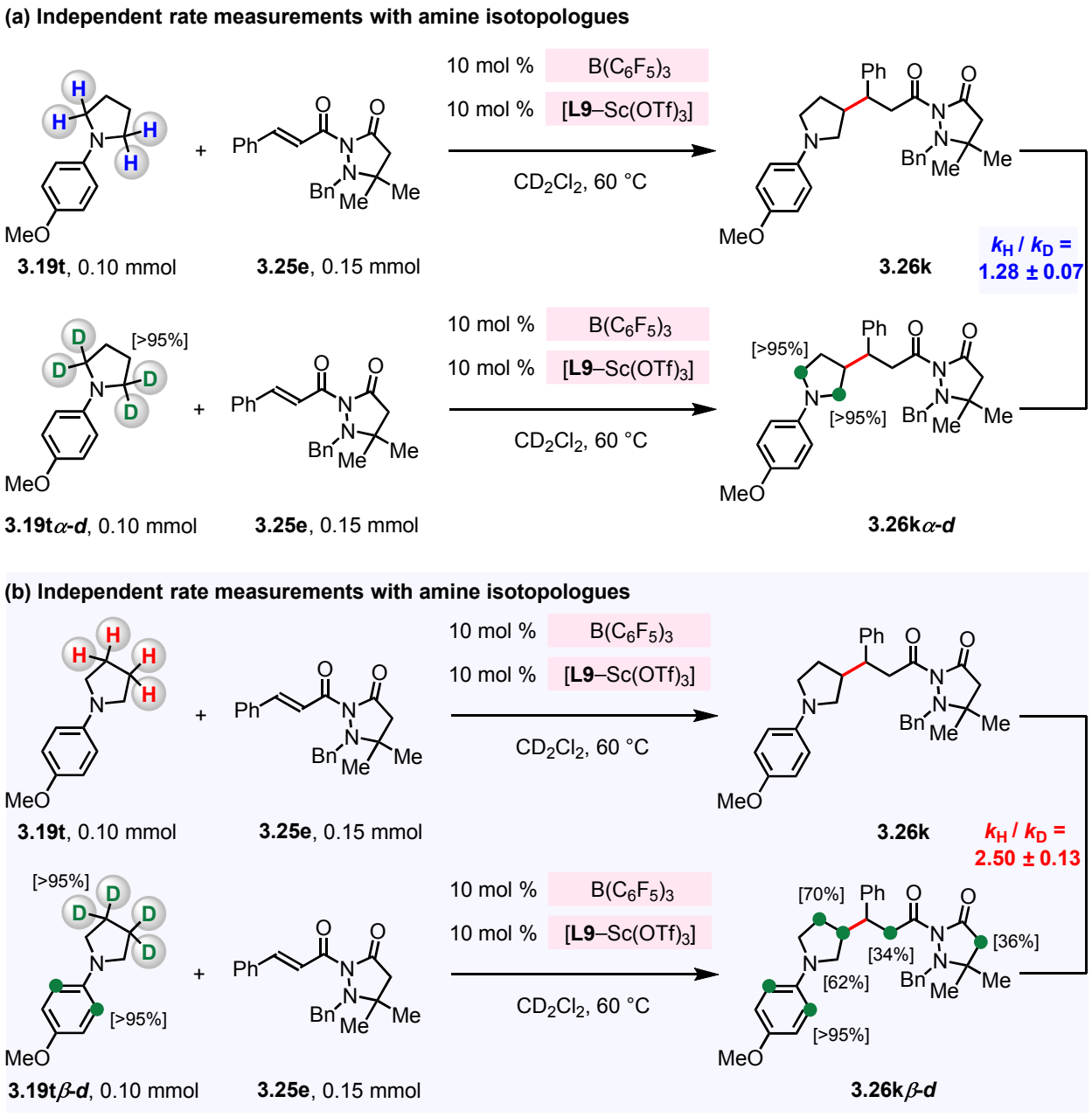
[21] (a) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066–3072. (b) Blackmond, D. G. *J. Am. Chem. Soc*. **2015**, *137*, 10852–10866.

found to have k_H/k_D = 1.28 ± 0.07. These results suggest that $B(C_6F_5)_3$ catalyzed hydride abstraction step is not the turnover-limiting step. We then carried out independent kinetic isotope effect experiments at the β-position. Comparison of the reaction rate between **3.19t** and **3.19t*β-d*** (Scheme 3.15b) revealed that **3.19t** reacts 2.5 times faster than **3.19t*β-d*** (k_H/k_D = 2.50 ± 0.13). These KIE experiments support the notion that the turnover-limiting step is the deprotonation step (Scheme 3.11, **XV** → **XVI**) which entails the cleavage of α-imino C–H or C–D bonds.

Figure 3.2. Determination of Reaction Orders



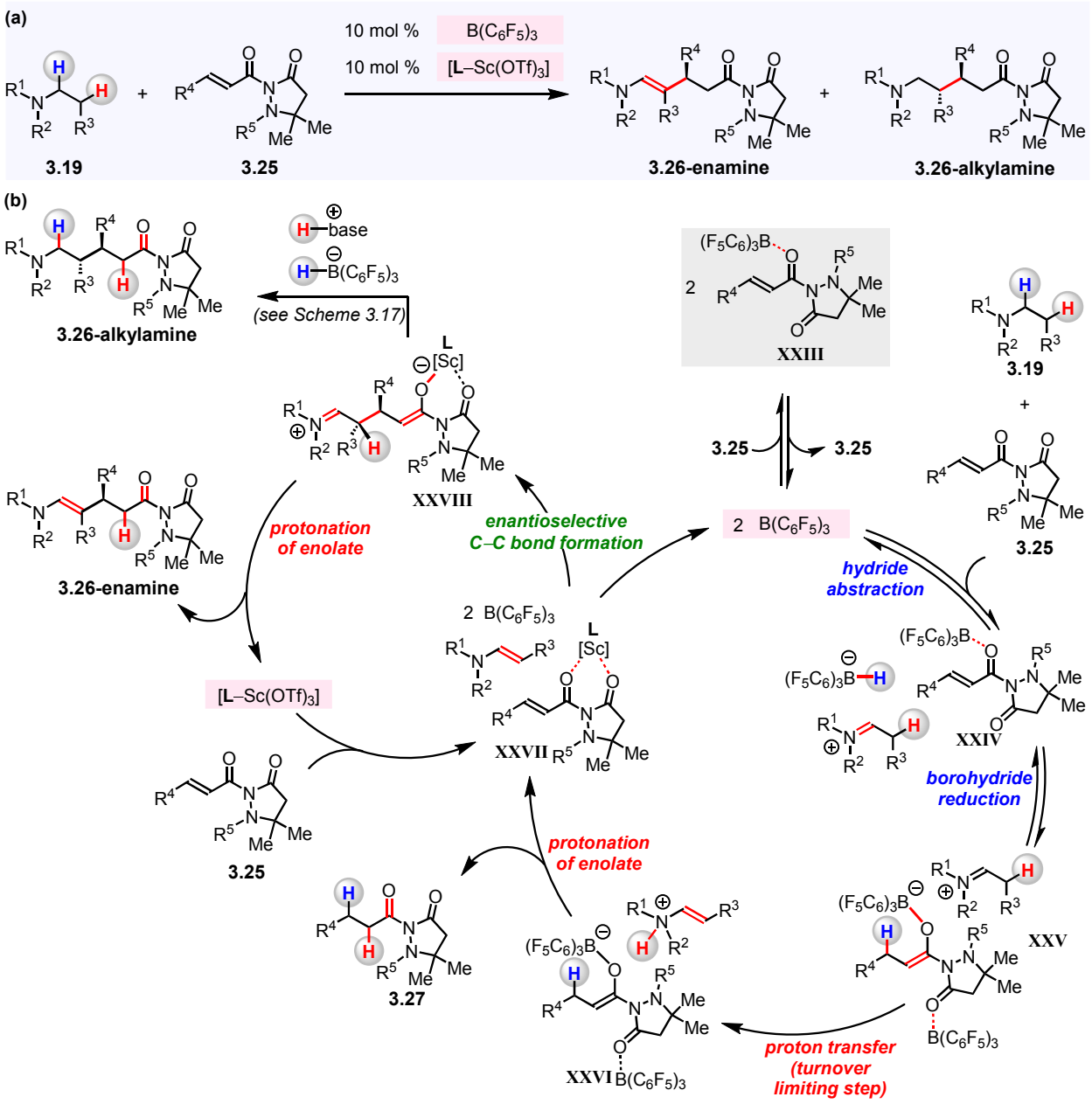
Scheme 3.15. Kinetic Isotope Effect Studies



The negative first-order dependence on the concentration of **3.25e** implies that the resting state consists of **3.25e** and the Lewis acid. Spectroscopic analysis of the reaction mixture (^{19}F NMR) supports the proposal in regard to formation of [**3.25e**–$B(C_6F_5)_3$] (**XXIII**, Scheme 3.16).[22]

[22] Parks, D. J.; Piers, W. E. *J. Am. Chem. Soc.* **1996**, *118*, 9440–9441.

Scheme 3.16. A Catalytic Cycle Consistent with the Results of Mechanistic Investigations



Since we also observe the reaction rate has a second-order dependence on $B(C_6F_5)_3$ concentration, this suggests there are two $B(C_6F_5)_3$ involved in the turnover-limiting step. If that is the case, the reaction rate should be reverse second-order dependence on the concentration of electrophile **3.25e.** The reverse first-order dependence implys that one electrophile **3.25e** is involved in the

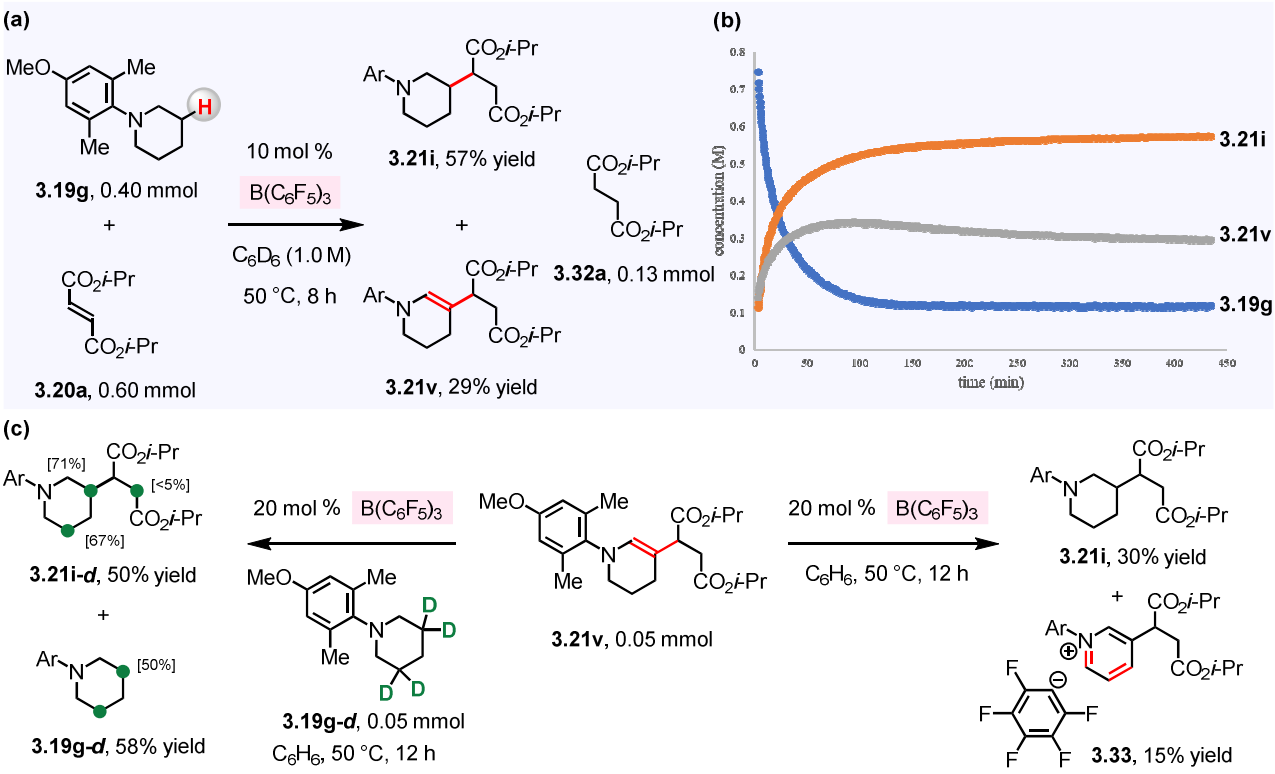
turnover-limiting step. Furthermore, since the reaction rate is first-order dependence on amine concentration of **3.19t**, amine **3.19t** is not responsible for the deprotonation of the iminium ion. Thus, it is likely that β-C–H alkylation proceeds through the release of free $B(C_6F_5)_3$ from **XXIII**, which then abstracts a hydride from **3.19** to form an iminium/borohydride complex (**XXIV**). Borohydride reduction of $(F_5C_6)_3B$-activated **3.25** delivers a $[(F_5C_6)_3B\text{–enolate}]^-[\text{iminium}]^+$ complex (**XXIV** → **XXV**).[6e, 23] Subsequent isomerization of the iminium into an enammonium (**XXV** → **XXVI**) is likely the turnover-limiting step (see the Hammett studies, as well as the section 3.6.6).[24] Protonolysis of $[(F_5C_6)_3B\text{–enolate}]^-$ in **XXVI** releases $B(C_6F_5)_3$, **3.27**, and an enamine (**XXVII**). Then, enantioselective C–C bond forming reaction between the enamine and [**L**–$Sc(OTf)_3$]-activated electrophile **3.25** leads to a zwitterionic intermediate that bears an iminium and an enolate moiety (**XXVII** → **XXVIII**). Finally, proton transfer within **XXVIII** produces **3.26-enamine** and regenerates **L**–$Sc(OTf)_3$, thus closing the cycle. Alternatively, borohydride reduction of the iminium and protonation of the resulting enolate in **XXVIII** produces an *N*-alkylamine product (**3.26-alkylamine**), as illustrated by the studies described below.

β-Amino C–H alkylation products (Tables 3.2, 3.3 and 3.7) were obtained either as an enamine, an *N*-alkylamine, or a mixture of the two (e.g., **3.21r** and **3.21s**, Table 3.3). We proposed that *N*-alkylamine products were formed by transfer hydrogenation of **XXVIII** (**XXVIII** → **3.26-alkylamine**, Scheme 3.17a), or reduction of enamines (**3.26-enamine** → **3.26-alkylamine**). To identify each product's origins, we studied the progress of $(F_5C_6)_3B$-catalyzed reaction between *N*-arylpiperidine **3.19g** and **3.20a** (Scheme 3.17a), which gives a mixture of *N*-alkylamine **3.21i**

[23] Chen, G. Q.; Kehr, G.; Daniliuc, C. G.; Bursch, M.; Grimme, S.; Erker, G. *Chem. Eur. J.* **2017**, *23*, 4723–4729.
[24] (a) Sorgi, K. L.; Maryanoff, C. A.; McComsey, D. F.; Graden, D. W.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1990**, *112*, 3567–3579. (b) Han, J.; Lu, Z.; Flach, A. L.; Paton, R. S.; Hammond, G. B.; Xu, B. *Chem. Eur. J.* **2015**, *21*, 11687–11691. (c) Ashley, M. A.; Hirschi, J. S.; Izzo, J. A.; Vetticatt, M. J. *J. Am. Chem. Soc.* **2016**, *138*, 1756–1759.

(57% yield) and enamine **3.21v** (29% yield) using 0.4 mL of C_6D_6 (vs the process involving 1.6 mL of C_6H_6 which selectively gives **3.21i**; Tables 3.2). We found that there is minimal conversion of **3.21i** into **3.21v** as evidenced by the mostly unchanged concentration of **3.21v** once the *β*-alkylation reaction completed (2 h; Scheme 3.17b). These results are consistent with the scenario that **3.26-alkylamine** (Scheme 3.16b) is formed by transfer hydrogenation of **XXVIII** without the intermediacy of **3.26-enamine**. Nonetheless, the hydride and proton source of transfer hydrogenation remained to be identified.

Scheme 3.17. Origin of Enamine and *N*-Alkylamine Products

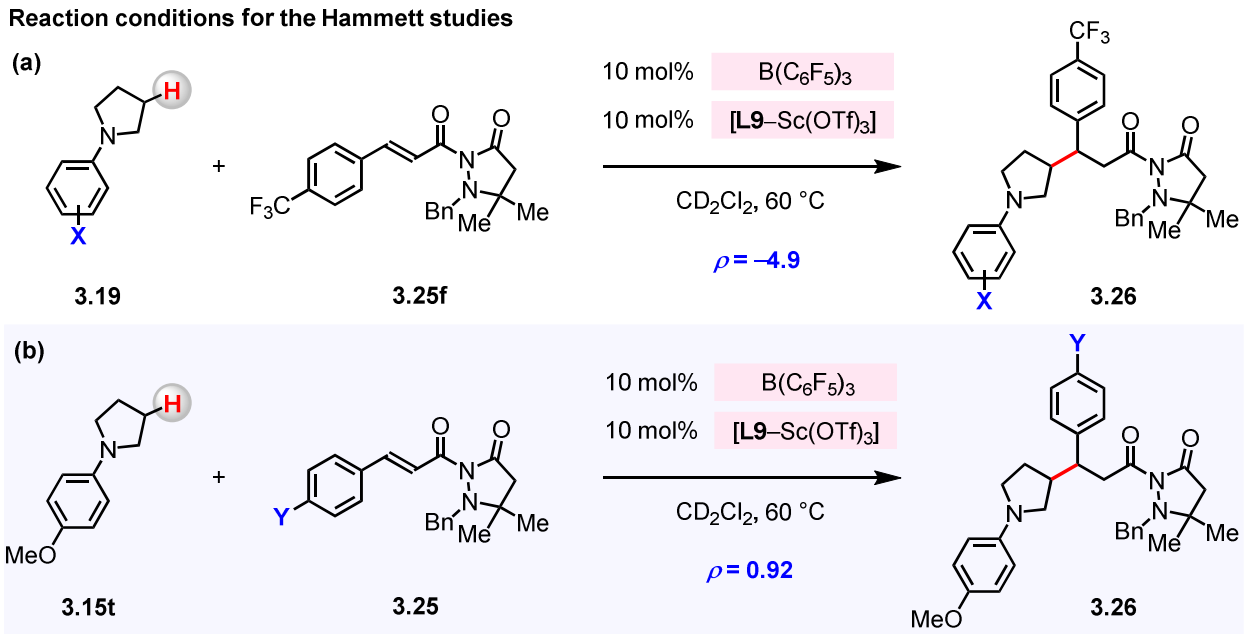


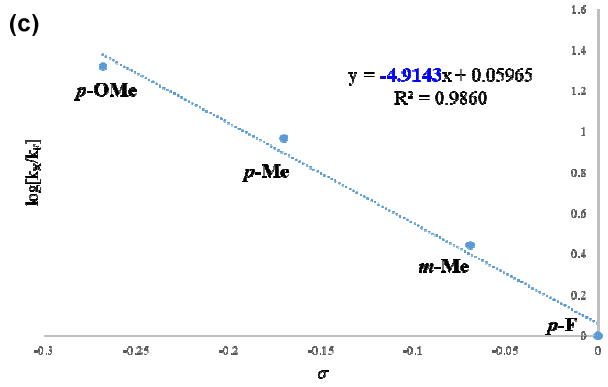
To probe further if, and under precisely what conditions **3.21v** can be converted to **3.21i**, we investigated the transformation of **3.21v** (isolated and purified by flash silica gel chromatography) in the presence of 20 mol% $B(C_6F_5)_3$ (C_6H_6, 12 h; Scheme 3.17c). There was 30% conversion to **3.21v**; in addition, $[pyridinium]^+[C_6F_5]^-$ (**3.33**, 15 %) was also produced.

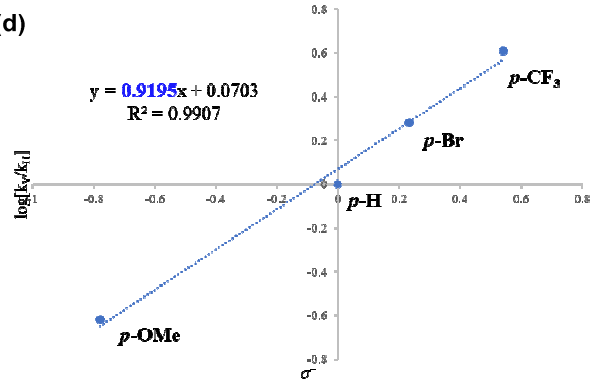
Treatment of **3.21v** with *N*-arylpiperidine-3,3,5,5-d_4 **3.19g-*d*** furnished **3.21i-*d*** in 50% yield, and not only was there significant deuterium incorporation at **C3** and **C5** positions of **3.21i-*d*** (71% and 67%, respectively), recovered **3.19g-*d*** had also undergone D/H exchange. These data suggest that $B(C_6F_5)_3$ can catalyze transfer hydrogenation of **3.21v** in the presence of another molecule of **3.21v** and/or **3.19g-*d*** serving as sources of H^+ (or D^+) and hydride (Scheme 3.17c). Nevertheless, under the standard conditions for $(F_5C_6)_3B$-catalyzed β-C–H alkylation reaction (Schemes 3.16 and 3.17), in situ generated $[(F_5C_6)_3B–H]^-[Base–H]^+$ (derived from the reaction of $B(C_6F_5)_3$ and *N*-alkylamine **3.19**) appears to react with either a highly reactive zwitterionic intermediate (**XXVIII** $\rightarrow$ **3.26-alkylamine**) or $(F_5C_6)_3B$-activated α,β-unsaturated compounds (**XXIV** $\rightarrow$ **XXV** $\rightarrow$ **XXVI** $\rightarrow$ **3.27**). As a consequence, hydrogenation of the relatively unreactive enamine **3.21v** to give **3.21i** may be outcompeted by these more facile processes.

Hammett studies revealed a strong dependence of the reaction rate on the electronic properties of the *N*-alkylamines, with *N*-arylpyrrolidine derivatives (**3.19**) bearing electron-donating substituents reacting more rapidly (ρ = –4.9, Schemes 3.18a and 3.18c). The large negative ρ value obtained supports the proposed mechanism (Scheme 3.16) in which $B(C_6F_5)_3$ abstracts a hydride from *N*-arylpyrrolidine **3.19** into a *N*-aryl iminium cation (**3.19** $\rightarrow$ **XXIV**), and its isomerization into an enammonium species (**XXIV** $\rightarrow$ **XXV** $\rightarrow$ **XXVI**); these processes take place at or prior to the turnover-limiting step. While the reaction rate was found to be less dependent of the electronic properties of α,β-unsaturated compounds **3.25**, those involving more electron-withdrawing groups reacted with higher efficiency (ρ = 0.92, Schemes 3.18b and 3.18d). This latter outcome is consistent with the hypothesis that **3.25** reacts with in situ generated $[(F_5C_6)_3B–H]^-$ to afford a boron–enolate intermediate (Scheme 3.16; **XXIV** $\rightarrow$ **XXV**), and that this hydride transfer also occurs at or prior to the turnover-limiting step.

Scheme 3.18. Hammett Studies







3.5. Conclusions and Future Outlook

In summary, we have developed a cooperative catalyst system consisting of $B(C_6F_5)_3$ and a chiral Sc-based complex for enantioselective β-amino C–H functionalization to generate enantioenriched δ-amino carbonyl compounds. We found that the cooperative funtions of $B(C_6F_5)_3$ and a chiral Sc-based complex can convert an *N*-alkylamine into a nucleophilic enamine and then promote its enantio- and diastereo-selective reaction with an α,β-unsaturated compound. Furthermore, this method is applicable to late-stage modification of bioactive trialkylamine molecules that contain various acid-sensitive function groups. Mechanistic investigations reveal that the turnover-limiting step is likely the isomerization of *N*-alkylamine-derived iminium ion into an enammonium intermediate.

The principles outlined above demonstrated that the use of an achiral Lewis acid and a chiral Lewis acid that may possess overlapping functions enables the chemo- and enantioselective β-amino C–H alkylation. It provides a rational basis for future development of processes for late-stage stereoselective β-amino C–H functionalization of multifunctional bioactive amines.

3.6. Expeirimental

3.6.1. Procedures, Materials and Instrumentation

General Experimental Procedures. All reactions were performed in standard, oven-dried glassware fitted with rubber septa under an inert atmosphere of nitrogen unless otherwise described. Stainless steel syringes or cannulas were used to transfer air- and moisture-sensitive liquids. Reported concentrations refer to solution volumes at room temperature. Evaporation and concentration *in vacuo* were performed using house vacuum (ca. 40 mm Hg). Column chromatography was performed with SiliaFlash® 60 (40–63 micron) silica gel from Silicycle. Thin layer chromatography (TLC) was used for reaction monitoring and product detection using pre-coated glass plates covered with 0.25 mm silica gel with fluorescent indicator; visualization by UV light (λ_{ex} = 254 nm) or $KMnO_4$ stain.

Materials. Reagents were purchased in reagent grade from commercial suppliers and used without further purification, unless otherwise described. Tris(pentafluorophenyl)borane was purchased from TCI and used without further purification. H_2O, in synthetic procedures, refers to distilled water. Chiral ligands **L1-L12** were prepared according to the procedures previously reported in the literature.[25] Amines and α,β-unsaturated compounds were prepared according to the procedures reported previously.[6e, 6f, 12g, 12h, 26]

[25] (a) Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jørgensen, K. A. *Chem*. *Eur*. *J*. **2002**, *8*, 1888−1898. (b) Tse, M. D.; Bhor, S.; Klawonn, M.; Anilkumar, G.; Jiao, H.; Döbler, C.; Spannenberg, A.; Mägerlein, W.; Hugl, H.; Beller, M. *Chem*. *Eur*. *J*. **2006**, *12*, 1855−1874. (c) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem*. *Rev*. **2011**, *111*, 284–437. (d) Itoh, K.; Sibi, M. P. *Org*. *Biomol*. *Chem*. **2018**, *16*, 5551−5565.

[26] (a) Takasu, N.; Oisaki, K.; Kanai, M. *Org. Lett*. **2013**, *15*, 1918−1921. (b) Kawamoto, K.; Zhong, M.; Wang, R.; Olsen, B. D.; Johnson, J. A. *Macromolecules* **2015**, *48*, 8980–8988. (c) Schmidt, W.; Vögtle, F.; Poetsch, E. *Liebigs Ann.* **1995**, 1319–1326. (d) Jiang, X.; Wei, X.; Lin, F.; Zhang, Z.; Yao, G.; Yang, S.; Zhao, W.; Zhao, C.; Xu, H. *Eur. J. Org. Chem*. **2020**, 3997–4003. (e) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718–719. (f) Ruiz Espelt, L.; McPherson, I. S.; Wiensch, E. M.; Yoon, T. P. *J. Am. Chem. Soc.* **2015**, *137*, 2452–2455.

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra and proton-decoupled carbon nuclear magnetic resonance (^{13}C {^{1}H} NMR) spectra were recorded at 25 °C (unless stated otherwise) on Inova 600 (600 MHz), Varian Unity/Inova 500 (500 MHz) or Oxford AS400 (400 MHz) spectrometers at the Boston College nuclear magnetic resonance facility. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to 0 ppm. Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent. The peak positions are quoted to one decimal place unless they are indistinguishable. The solvent peak was referenced to 77.2 ppm for ^{13}C for $CDCl_3$. Benzotrifluoride was used as an external standard for ^{19}F NMR and referenced to −63.7 ppm. Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz). Infrared spectra were recorded on a Bruker FT-IR Alpha (ATR mode) spectrophotometer. Data are represented as follows: frequency of absorption (cm^{-1}). High-resolution mass spectrometry was performed on a JEOL AccuTOF-DART (positive mode) at the Mass Spectrometry Facility, Boston College.

Abbreviations used. Bn = benzyl, Boc = *tert*-butoxycarbonyl, COD = 1,5-cyclooctadiene, COSY = correlation spectroscopy, DART = direct analysis in real time, DCM = dichloromethane, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, er = enantiomeric ratio, HPLC = high pressure liquid chromatography, Et_3N = trimethylamine, EtOAc = ethyl acetate, HR = high-resolution, HSQC = heteronuclear single quantum coherence, LC = liquid chromatography, MS = mass spectrometry, NOESY = nuclear Overhauser effect spectroscopy, OTf = triflate, PMP = *p*-methoxyphenyl, PTLC = preparatory thin-layer chromatography, TBAF = tetra-*n*-butylammonium fluoride, TBME = *tert*-butyl methyl ether, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran,

TLC = thin-layer chromatography, TMS = trimethylsilyl, TOF = time-of-flight.

3.6.2. Experimental Section

3.6.2.1 Substrate Preparation

3.6.2.1.1 Preparation of Amine Substrates (Table S1)

Substrates **3.19** were prepared according to the literature procedures. [6e, 6f, 12g, 12h, 25] Methods used to prepare the newly synthesized amines (**3.19d**, **3.19f**, **3.19g-*d*, 3.19h, 3.19l, 3.19m, 3.19o, 3.19t*α*-*d*** and **3.19t*β*-*d***) and their spectroscopic data are provided below.

Table S1A. List of Amine Substrates

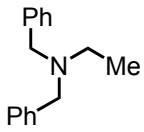
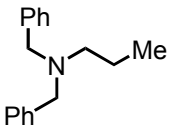
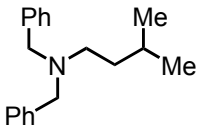
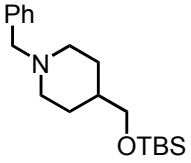
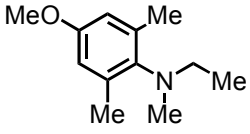
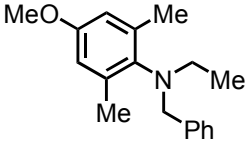
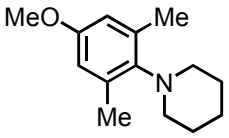
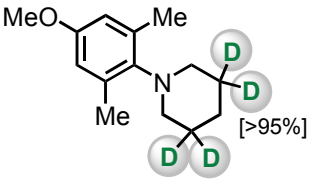
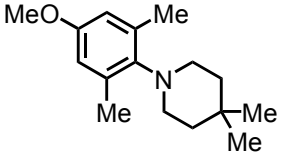
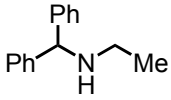
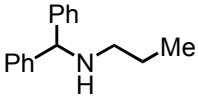
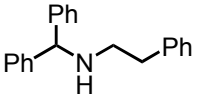
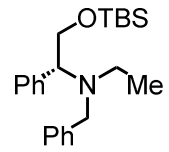
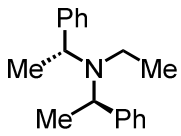
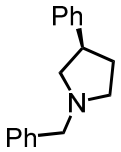
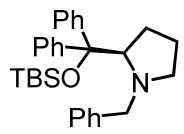
			
3.19a	**3.19b**	**3.19c**	**3.19d**
			
3.19e	**3.19f**	**3.19g**	**3.19g-*d***
			
3.19h	**3.19i**	**3.19j**	**3.19k**

Table S1B. List of Amine Substrates

			
3.19l	**3.19m**	**3.19n**	**3.19o**

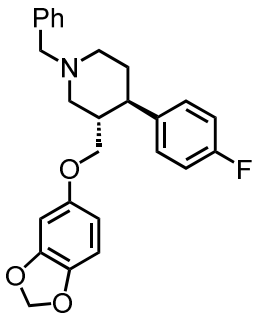
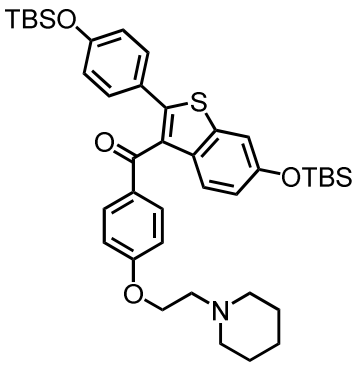
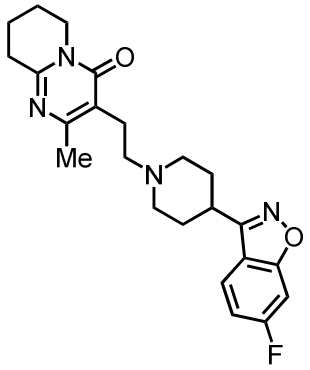
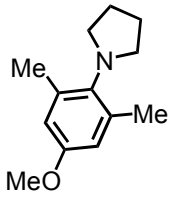
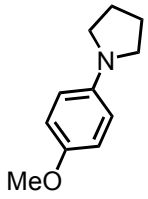
		
3.19p	**3.19q**	**3.19r**

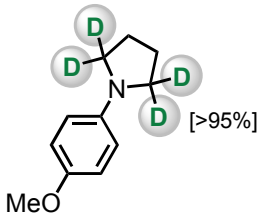
Table S1C. List of Amine Substrates



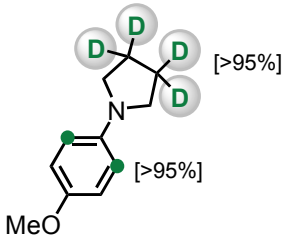
3.19s



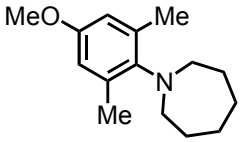
3.19t



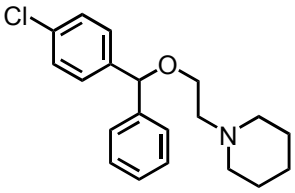
3.19tα-*d*



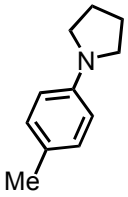
3.19tβ-*d*



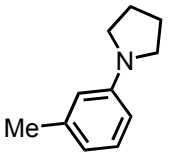
3.19u



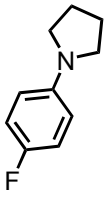
3.19v



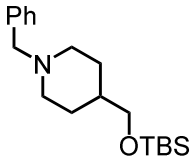
3.19w



3.19x



3.19y

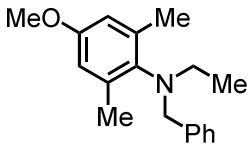


3.19d

1-Benzyl-4-(((*tert*-butyldimethylsilyl)oxy)methyl)piperidine (3.19d)

1-Benzyl-4-(((*tert*-butyldimethylsilyl)oxy)methyl)piperidine was prepared following the General Procedure for the TBS Protection of Alcohols using (1-benzylpiperidin-4-yl)methanol (10 mmol) as the alcohol. The unpurified product was subjected to silica gel column chromatography (ethyl ether:hexanes = 1:4) to afford **3.19d** as a colorless liquid (3.0 g, 94%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 4H), 7.26 (s, 1H), 3.49 (s, 2H), 3.43 (d, J = 6.5 Hz, 2H), 2.88 (dt, J = 11.6, 3.3 Hz, 2H), 1.93 (td, J = 11.7, 2.5 Hz, 2H), 1.73 – 1.63 (m, 2H), 1.46 (ddd, J = 11.4, 7.5, 4.5 Hz, 1H), 1.28 – 1.16 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H).

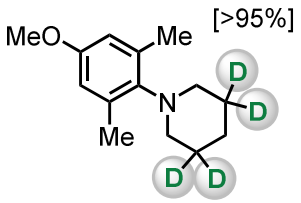


3.19f

***N*-Benzyl-*N*-ethyl-4-methoxy-2,6-dimethylaniline (3.19f)**

N-Benzyl-*N*-ethyl-4-methoxy-2,6-dimethylaniline was prepared following the General Procedure for the Alkylation of Amines using *N*-ethyl-4-methoxy-2,6-dimethylaniline[2] (0.9 g, 5.0 mmol), benzyl bromide (1.5 equiv.) and K_2CO_3 (2.0 equiv.). The unpurified product was subjected to silica gel column chromatography (ethyl ether:hexanes = 1:19) to afford **3.19f** as a colorless liquid (1.2 g, 88%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 4H), 7.26 – 7.18 (m, 1H), 6.55 (s, 2H), 4.13 (s, 2H), 3.75 (d, J = 1.4 Hz, 3H), 3.08 – 2.94 (m, 2H), 2.28 (s, 6H), 0.92 (t, J = 7.2 Hz, 3H).

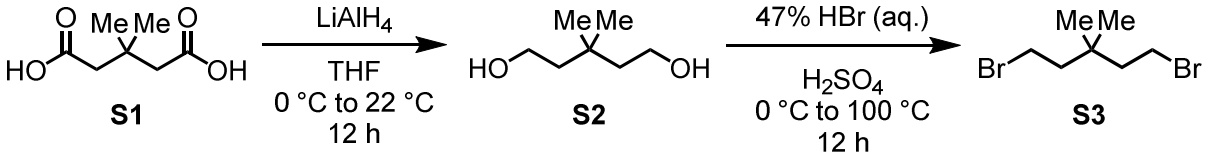


1j-*d*

1-(4-Methoxy-2,6-dimethylphenyl)piperidine-3,3,5,5-d_4 (3.19g-*d*)

3.19g-*d* was prepared following the previously reported literature,[12h] using 1-(4-Methoxy-2,6-dimethylphenyl)piperidine (877 mg, 4.0 mmol), acetone-d_6 (2.0 mL, 28 mmol) and $B(C_6F_5)_3$ (102 mg, 0.20 mmol). The crude reaction mixture was subjected to silica gel chromatography (ethyl ether:hexanes = 1:20) to give the product **3.19g-*d*** as a yellow liquid with 88% *d*-incorporation at the *β*-amino position. This compound was resubjected to the aforementioned reaction conditions and after flash silica gel column chromatography (ethyl ether:hexanes = 1:20), **3.19g-*d*** was obtained with >95% *d*-incorporation level at the *β*-amino position. (0.63 g, 70%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 6.69 – 6.35 (m, 2H), 3.77 – 3.71 (m, 3H), 3.15 – 2.74 (m, 4H), 2.43 – 2.15 (m, 6H), 1.63 – 1.57 (m, 0.19H, >95%D), 1.56 – 1.47 (m, 2H).

Synthesis of 1,5-Dibromo-3,3-dimethylpentane (S3)



1,5-Dibromo-3,3-dimethylpentane (**S3**) was prepared following the literature previously reported.[26d]

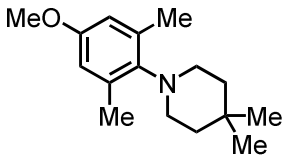
3,3-Dimethylpentane-1,5-diol (S2)

To a solution of 3,3-dimethylpentanedioic acid **S1** (3.0 g, 18.7 mmol) in THF, $LiAlH_4$ was added portionwise at 0 °C. The reaction mixture was slowly warmed to 22 °C and was allowed to stir for

12 hours. Upon completion of the reaction (monitored by TLC), the mixture was quenched with 1.0 M NaOH (aq.) at 0 °C and extracted with EtOAc (3 x 50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The unpurified product was subjected to flash silica gel column chromatography (EtOAc:hexanes = 1:1) to give 3,3-dimethylpentane-1,5-diol **S2** as a colorless liquid (1.8 g, 73%). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 3.74 (t, *J* = 7.1 Hz, 4H), 1.58 (t, *J* = 7.0 Hz, 4H), 0.95 (s, 6H).

1,5-Dibromo-3,3-dimethylpentane (S3)

To a solution of 3,3-dimethylpentane-1,5-diol **S2** (1.2 g, 9.4 mmol) in 47% HBr (aq.), H_2SO_4 was added dropwise at 0 °C. The reaction mixture was slowly heated to 100 °C and was allowed to stir for 12 hours. Upon completion of the reaction (monitored by TLC), the mixture was quenched with $NaHCO_3$ (aq.) and extracted with ethyl ether (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The unpurified product was then subjected to flash silica gel column chromatography (100% hexanes) to afford 1,5-dibromo-3,3-dimethylpentane **S3** as a colorless liquid (1.8 g, 75%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.41 – 3.33 (m, 4H), 1.90 – 1.82 (m, 4H), 0.94 (s, 6H).

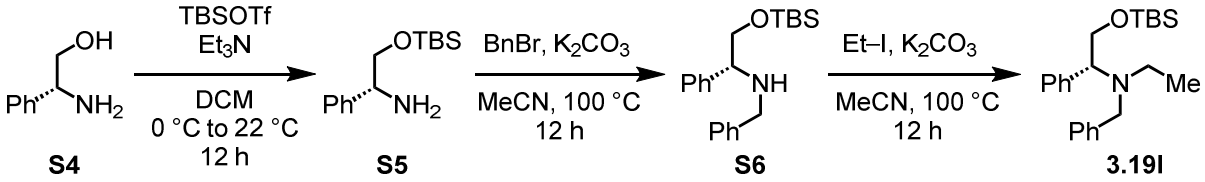


3.19h

1-(4-Methoxy-2,6-dimethylphenyl)-4,4-dimethylpiperidine (3.19h)

3.19h was prepared through the reaction of 4-methoxy-2,6-dimethylaniline (0.7 g, 4.7 mmol), 1,5-dibromo-3,3-dimethylpentane (1.5 equiv.) and K_2CO_3 (4.0 equiv.) in MeCN. The reaction mixture in pressure vessel was placed in an oil bath at 100 °C and was allowed to stir for 12 hours. Upon

completion (monitored by TLC), the solution was cooled to 22 °C. H_2O was then added and the organic material was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The unpurified product mixture was subjected to flash silica gel column chromatography (ethyl ether:hexanes = 1:49) to afford **3.19h** as a colorless liquid (0.7 g, 61%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 6.53 (s, 2H), 3.74 (s, 3H), 3.01 – 2.94 (m, 4H), 2.30 (s, 6H), 1.47 – 1.39 (m, 4H), 0.98 (s, 6H).



(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-phenylethan-1-amine (S5)

(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-phenylethan-1-amine was prepared from (*R*)-2-amino-2-phenylethan-1-ol **S4** following the General Procedure for the TBS Protection of Alcohols on a 21.8 mmol scale. The unpurified product was subjected to silica gel column chromatography (EtOAc:hexanes = 1:9) to afford **S5** as a yellow liquid (3.2 g, 58%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 6.4 Hz, 2H), 4.07 (dd, *J* = 8.4, 4.0 Hz, 1H), 3.72 (dd, *J* = 9.8, 4.0 Hz, 1H), 3.52 (dd, *J* = 9.8, 8.4 Hz, 1H), 1.81 (br, 2H), 0.90 (s, 9H), 0.02 (s, 6H).

(*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethan-1-amine (S6)

(*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethan-1-amine was prepared following the General Procedure for the Alkylation of Amines using (*R*)-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethan-1-amine (12.5 g, 49.7 mmol), (bromomethyl)benzene (0.9 equiv.) and K_2CO_3 (1.5 equiv.). The unpurified product was subjected to silica gel column chromatography (ethyl

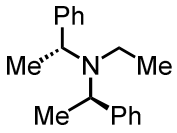
ether:hexanes = 1:9) to afford **S6** as a colorless liquid (13.8 g, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 6.8 Hz, 2H), 7.37 – 7.26 (m, 7H), 7.25 – 7.20 (m, 1H), 3.81 (dd, *J* = 9.1, 4.0 Hz, 1H), 3.75 (d, *J* = 13.6 Hz, 1H), 3.66 (dd, *J* = 9.9, 4.0 Hz, 1H), 3.61 – 3.52 (m, 2H), 0.88 (s, 9H), 0.01 (s, 3H), -0.00 (s, 3H).

(*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-ethyl-1-phenylethan-1-amine (3.19l)

(*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-ethyl-1-phenylethan-1-amine was prepared following the General Procedure for the Alkylation of Amines using (*R*)-*N*-benzyl-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethan-1-amine (5.5 g, 16.1 mmol), iodoethane (1.5 equiv.) and K_2CO_3 (2.0 equiv.). The unpurified product was subjected to silica gel column chromatography (ethyl ether:hexanes = 1:19) to afford **3.19l** as a colorless liquid (4.3 g, 72%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.4 Hz, 4H), 7.30 (dt, *J* = 11.2, 7.5 Hz, 4H), 7.21 (dt, *J* = 14.5, 7.3 Hz, 2H), 4.05 (dd, *J* = 10.1, 5.7 Hz, 1H), 3.95 – 3.83 (m, 2H), 3.76 (d, *J* = 14.3 Hz, 1H), 3.57 (d, *J* = 14.3 Hz, 1H), 2.71 (dq, *J* = 14.0, 7.1 Hz, 1H), 2.48 (dq, *J* = 13.9, 7.0 Hz, 1H), 1.00 (t, *J* = 7.0 Hz, 3H), 0.82 (s, 9H), -0.04 (s, 3H), -0.06 (s, 3H).

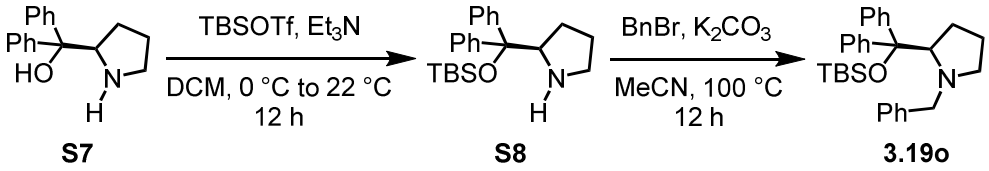


3.19m

(*R*)-*N*-Ethyl-1-phenyl-*N*-((*R*)-1-phenylethyl)ethan-1-amine (3.19m)

3.19m was prepared through the reaction of (*R*)-bis((*R*)-1-phenylethyl)amine (2.7 g, 11.8 mmol), iodoethane (1.5 equiv.) and K_2CO_3 (2.0 equiv.) in MeCN. The reaction mixture in pressure vessel was placed in an oil bath at 100 °C and was allowed to stir for 12 hours. Upon completion

(monitored by TLC), the solution was allowed to cool to 22 °C. H_2O was then added and the organic material was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The unpurified product mixture was subjected to flash silica gel column chromatography (ethyl ether:hexanes = 1:19) to afford **1g** as a colorless liquid (2.1 g, 70%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.38 (d, *J* = 7.6 Hz, 4H), 7.29 (t, *J* = 7.6 Hz, 4H), 7.20 (t, *J* = 7.2 Hz, 2H), 4.01 (q, *J* = 6.8 Hz, 2H), 2.67 (dq, *J* = 14.1, 7.0 Hz, 1H), 2.48 (dq, *J* = 14.2, 7.1 Hz, 1H), 1.38 (d, *J* = 6.9 Hz, 6H), 0.80 (t, *J* = 7.1 Hz, 3H).



S7 **S8** **3.19o**

(*R*)-2-(((*tert*-Butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine (S8)

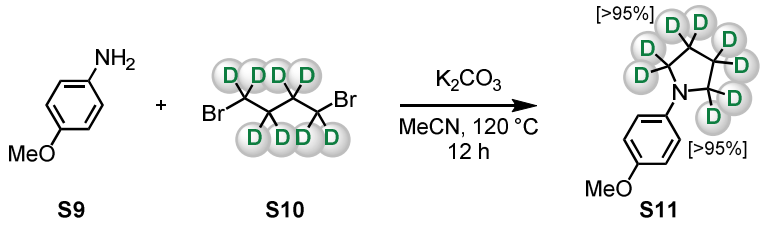
S8 was prepared through the TBS protection of (*R*)-diphenyl(pyrrolidin-2-yl)methanol (**S7**).

To a solution of **S7** (20 mmol) in DCM at 0 °C, Et_3N (1.3 equiv.) was added, followed by the dropwise addition of TBSOTf (1.3 equiv.). After the addition, the reaction mixture was allowed to warm to 22 °C and stirred for 12 hours. Upon completion (monitored by TLC), H_2O was added and the organic material was then extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The unpurified product mixture was subjected to flash silica gel column chromatography (ethyl ether:hexanes = 1:9) to afford **S8** as a colorless liquid (4.1 g, 56%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.52 (d, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.32 – 7.17 (m, 6H), 4.01 (t, *J* = 7.3 Hz, 1H), 2.88 – 2.76 (m, 1H), 2.76 – 2.64 (m, 1H), 1.59 (q, *J* = 7.5 Hz, 2H), 1.55 – 1.46 (m, 1H), 1.30 – 1.12 (m, 1H), 0.95 (s, 9H), -0.21 (s, 3H), -0.46 (s, 3H).

(*R*)-1-Benzyl-2-(((*tert*-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine (3.19o)

3.19o was prepared through the reaction of **S8** (1.5 g, 4.1 mmol), benzyl bromide (1.1 equiv.) and K_2CO_3 (4.0 equiv.) in MeCN. The reaction mixture in pressure vessel was placed in an oil bath at 100 °C and was allowed to stir for 12 hours. Upon completion (monitored by TLC), the solution was cooled to 22 °C. H_2O was then added and the organic material was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The unpurified product mixture was subjected to flash silica gel column chromatography (ethyl ether:hexanes = 1:19) to afford **3.19o** as a colorless liquid (1.45 g, 78%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.64 (dd, *J* = 7.6, 2.2 Hz, 2H), 7.55 (dd, *J* = 8.0, 1.8 Hz, 2H), 7.32 – 7.25 (m, 6H), 7.25 – 7.19 (m, 2H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 2H), 4.36 (d, *J* = 13.3 Hz, 1H), 4.00 (dd, *J* = 9.4, 4.1 Hz, 1H), 3.45 (d, *J* = 13.3 Hz, 1H), 2.30 (td, *J* = 6.5, 3.4 Hz, 1H), 2.12 (td, *J* = 9.2, 6.6 Hz, 1H), 1.99 (dd, *J* = 13.4, 8.9 Hz, 1H), 1.87 (dd, *J* = 8.6, 4.3 Hz, 1H), 1.39 – 1.26 (m, 1H), 0.90 (s, 9H), 0.64 – 0.54 (m, 1H), -0.39 (s, 3H), -0.43 (s, 3H).

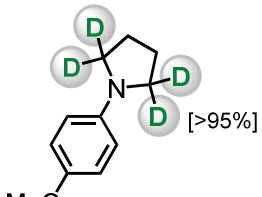
Synthesis of 1-(4-Methoxyphenyl)pyrrolidine-2,2,3,3,4,4,5,5-*d*$_8$ (S11)



S9 **S10** **S11**

1,4-Dibromobutane-1,1,2,2,3,3,4,4-*d*$_8$ (**S10**) was prepared following the literature previously reported.[26b] **S11** was prepared through the reaction of 4-methoxyaniline (1.2 g, 10 mmol), **S10** (2.0 g, 0.9 mmol) and K_2CO_3 (4.1 g, 30 mmol) in MeCN. The reaction mixture in pressure vessel was placed in an oil bath at 120 °C and was allowed to stir for 12 hours. Upon completion (monitored by TLC), the solution cooled to 22 °C. H_2O was then added and the organic material was extracted

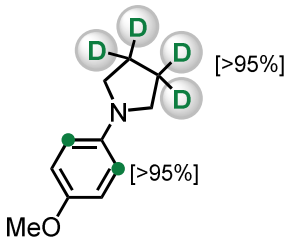
with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The unpurified product mixture was subjected to flash silica gel column chromatography (ethyl ether:hexanes = 1:20) to give the product **S11** as a white solid (1.1 g, 82%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.84 (d, J = 8.9 Hz, 2H), 6.53 (d, J = 9.0 Hz, 2H), 3.76 (s, 3H), 3.22 – 3.18 (m, 0.02H, >95%D), 1.96 – 1.91 (m, 0.03H, >95%D).



3.19tα-*d*

1-(4-Methoxyphenyl)pyrrolidine-2,2,5,5-d_4 (3.19tα-*d*)

3.19tα-*d* was prepared following a method previously reported in the literature[12h] using **S11** (556 mg, 3.0 mmol), acetone (1.5 mL, 20.4 mmol) and $B(C_6F_5)_3$ (154 mg, 0.30 mmol). The crude reaction mixture was subjected to silica gel chromatography (ethyl ether:hexanes = 1:20) to give the product **3.19tα-*d*** as a yellow liquid with >95% and 40% *d*-incorporation at the α- and β-amino position, respectively. This compound was resubjected to the aforementioned reaction conditions and after flash silica gel column chromatography (ethyl ether:hexanes = 1:20), **3.19tα-*d*** was obtained with >95% and <5% *d*-incorporation level at the α- and β-amino position. (501 mg, 80%). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.90 – 6.78 (m, 2H), 6.60 – 6.46 (m, 2H), 3.76 (s, 3H), 3.23 – 3.19 (m, 0.02H, >95%D), 2.05 – 1.88 (m, 4H).



3.19t*β*-*d*

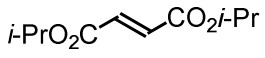
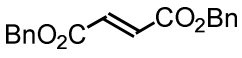
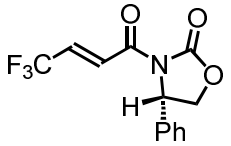
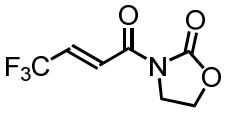
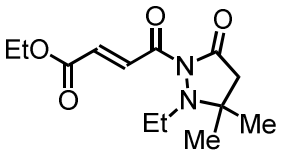
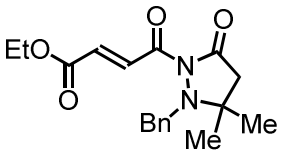
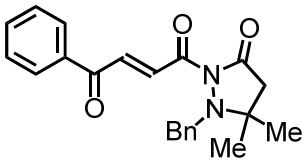
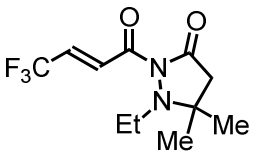
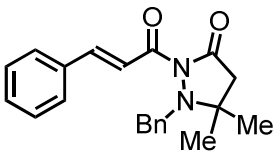
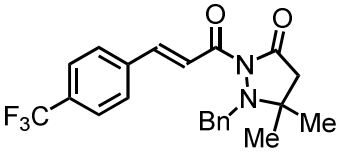
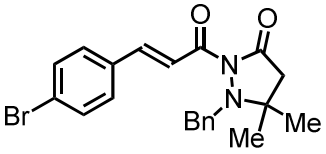
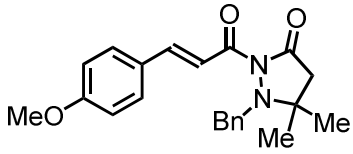
1-(4-Methoxyphenyl-2,6-d_2)pyrrolidine-3,3,4,4-d_4 (3.19t*β*-*d*)

3.19t*β*-*d* was prepared following a method previously reported in the literature[12h] using 1-(4-methoxyphenyl)pyrrolidine (886 mg, 5.0 mmol), acetone-d_6 (2.5 mL, 35 mmol) and $B(C_6F_5)_3$ (128 mg, 0.25 mmol). The crude reaction mixture was subjected to silica gel chromatography (ethyl ether:hexanes = 1:20) to give the product **3.19t*β*-*d*** as a yellow liquid with 70% *d*-incorporation at the *β*-amino position. This compound was resubjected to the aforementioned reaction conditions and after flash silica gel column chromatography (ethyl ether:hexanes = 1:20), **3.19t*β*-*d*** was obtained with >95% *d*-incorporation level at the *β*-amino position. (686 mg, 74%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.84 (s, 2H), 6.56 – 6.51 (m, 0.02H, >95%D), 3.76 (s, 3H), 3.33 – 3.12 (m, 4H), 1.98 – 1.93 (m, 0.15H, >95%D).

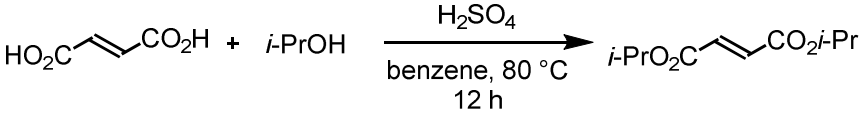
3.6.2.1.2. Preparation of α,β-Unsaturated Compounds

α,β-Unsaturated compounds were prepared following the methods reported in the literature[26d-26f] and as described below.

Table S2. List of α,β-Unsaturated Compounds

		
3.20a	**3.20b**	**3.23b**
		
3.23c	**3.25a**	**3.25b**
		
3.25c	**3.25d**	**3.25e**
		
3.25f	**3.25g**	**3.25h**

Preparation of Diisopropyl Fumarate (3.20a)

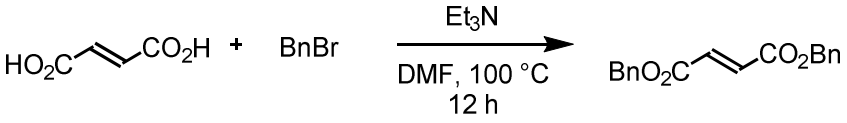


fumaric acid **3.20a**

Diisopropyl fumarate was prepared according to a procedure reported previously in the literature. A mixture of fumaric acid (23.2 g, 200 mmol), isopropyl alcohol (4.0 equiv.), H_2SO_4 (2.0 mL) and

benzene (25.0 mL) was heated at 80 °C and was allowed to stir for 12 hours. The reaction mixture was quenched with $NaHCO_3$ (aq.) at 0 °C and extracted with ethyl ether (3 x 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The unpurified product mixture was distilled (75 °C, 40 mmHg) to give diisopropyl fumarate **3.20a** as a colorless liquid (24.0 g, 60%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 6.81 (s, 2H), 5.11 (hept, J = 6.2 Hz, 2H), 1.29 (d, J = 6.3 Hz, 12H).

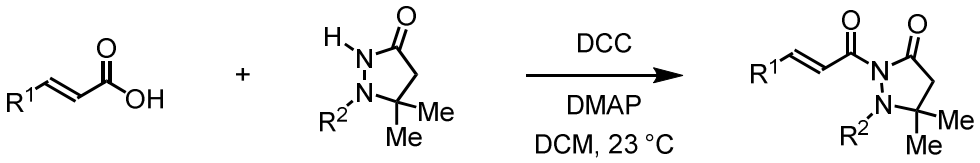
Preparation of Dibenzyl Fumarate (3.20b)



fumaric acid **3.20b**

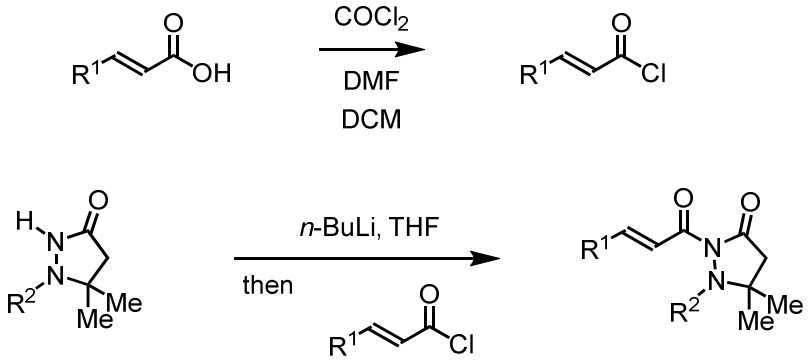
Dibenzyl fumarate was prepared according to a procedure reported previously in the literature.[26d] To a solution of fumaric acid (6.0 g, 51.7 mmol) in DMF (6 mL), Et_3N (2.0 equiv) and (bromomethyl)benzene (1.9 equiv.) were added dropwise. The reaction mixture was allowed to stir at 100 °C for 12 hours. Upon completion, the reaction mixture was poured into cold water and then filtered to give a brown solid. The unpurified product was then subjected to silica gel column chromatography (EtOAc:hexanes = 3:17) and was further purified by recrystallization (EtOAc:hexanes = 1:20) to give dibenzyl fumarate **3.20b** as a white solid (8.2 g, 56%). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.41 – 7.30 (m, 10H), 6.92 (s, 2H), 5.23 (s, 4H).

General Procedure A for Preparation of 2-Acryloylpyrazolidinone Derivatives



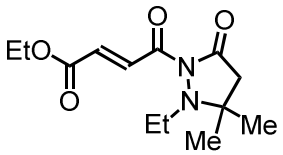
Corresponding carboxylic acid (1.0 eq.), pyrazolidinone[26e] (1.0 eq.) and 4-dimethylaminopyridine (0.1 eq) were dissolved in DCM at 22 °C. After *N*,*N*'-dicyclohexylcarbodiimide (1.1 eq) was added to the solution, it was allowed to stir overnight to afford the corresponding α,β-unsaturated compound. Upon completion, reaction mixture was filtered through Celite using DCM as solvent. The unpurified product mixture was subjected to flash silica gel column chromatography.

General Procedure B for Preparation of 2-Acryloylpyrazolidinone Derivatives



n-BuLi (1.1 eq.) was added to the appropriate pyrazolidinone in dry THF at –78 °C, and the mixture (**Mixture A**) was allowed to stir at –78 °C. Oxalyl chloride (3.0 eq.) was added dropwise into corresponding carboxylic acid (1.0 eq.) in DCM solution at 0 °C. 2 drops of DMF was added, and the mixture was allowed to stir for 1 hour. The solvent was removed under reduced pressure, and the residue was added into **Mixture A**. The mixture was stirred at –78 °C for 2-3 hours until the reaction was complete. The reaction was quenched with saturated aqueous ammonium chloride and THF was removed under reduced pressure. The residue was dissolved in DCM and washed with sat. $NaHCO_3$ (aq.). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and

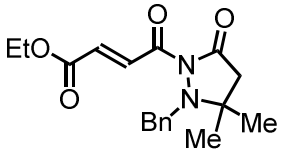
concentrated under reduced pressure. The unpurified product mixture was subjected to flash silica gel column chromatography.



3.25a

Ethyl (*E*)-4-(2-ethyl-3,3-dimethyl-5-oxopyrazolidin-1-yl)-4-oxobut-2-enoate (3.25a)

6c was prepared following **General Procedure B for Preparation of 2-Acryloylpyrazolidinone Derivatives** using (*E*)-4-ethoxy-4-oxobut-2-enoic acid (3.60 g, 25.0 mmol), 1-ethyl-5,5-dimethylpyrazolidin-3-one (3.60 g, 25.0 mmol), oxalyl chloride (9.52 g, 75 mmol) and *n*-BuLi (27.5 mmol). The unpurified product was subjected to flash silica gel column chromatography (EtOAc:hexanes = 1:3) to afford **3.25a** as a yellow liquid (4.5 g, 67%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.93 (d, *J* = 15.6 Hz, 1H), 6.96 (d, *J* = 15.6 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.01 (q, *J* = 7.1 Hz, 2H), 2.60 (s, 2H), 1.35 – 1.31 (m, 9H), 1.08 (t, *J* = 7.2 Hz, 3H).

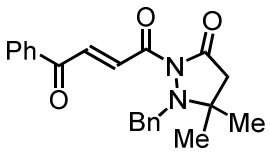


3.25b

Ethyl (*E*)-4-(2-benzyl-3,3-dimethyl-5-oxopyrazolidin-1-yl)-4-oxobut-2-enoate (3.25b)

3.25b was prepared following **General Procedure B for Preparation of 2-Acryloylpyrazolidinone Derivatives** using (*E*)-4-ethoxy-4-oxobut-2-enoic acid (5.04 g, 35.0 mmol), 1-benzyl-5,5-dimethylpyrazolidin-3-one (6.79 g, 35.0 mmol), oxalyl chloride (13.33 g, 105 mmol) and *n*-BuLi (38.5 mmol). The unpurified product was subjected to flash silica gel column chromatography (EtOAc:hexanes = 1:3) to afford **3.25b** as a yellow solid (5.0 g, 53%). **^{1}H**

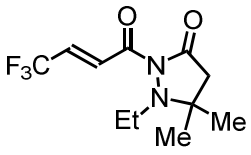
NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 15.5 Hz, 1H), 7.29 (d, *J* = 5.0 Hz, 2H), 7.26 – 7.22 (m, 3H), 6.49 (d, *J* = 15.5 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 2H), 2.61 (s, 2H), 1.34 (s, 6H), 1.30 (t, *J* = 7.1 Hz, 3H).



3.25c

(*E*)-1-(2-Benzyl-3,3-dimethyl-5-oxopyrazolidin-1-yl)-4-phenylbut-2-ene-1,4-dione (3.25c)

3.25c was prepared following **General Procedure A for Preparation of 2-Acryloylpyrazolidinone Derivatives** using (*E*)-4-oxo-4-phenylbut-2-enoic acid (2.64 g, 15.0 mmol), 1-benzyl-5,5-dimethylpyrazolidin-3-one (3.06 g, 15.0 mmol), *N,N′*-dicyclohexylcarbodiimide (3.30g, 16.5 mmol) and dimethylaminopyridine (0.18 g, 1.5 mmol). The unpurified product was subjected to flash silica gel column chromatography (Et_3N:EtOAc:hexanes = 1:30:90) to afford **3.25c** as a yellow solid (1.5 g, 26%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.92 (d, *J* = 7.8 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 3H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.25 (s, 1H), 7.19 (t, *J* = 7.5 Hz, 2H), 7.11 (t, *J* = 7.3 Hz, 1H), 4.01 (s, 2H), 2.64 (s, 2H), 1.37 (s, 6H).

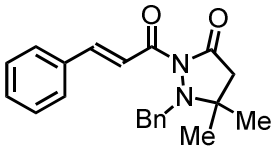


3.25d

(*E*)-1-Ethyl-5,5-dimethyl-2-(4,4,4-trifluorobut-2-enoyl)pyrazolidin-3-one (3.25d)

3.25d was prepared following **General Procedure A for Preparation of 2-Acryloylpyrazolidinone Derivatives** using (*E*)-4,4,4-trifluorobut-2-enoic acid (2.52 g, 18.0 mmol), 1-ethyl-5,5-dimethylpyrazolidin-3-one (2.66 g, 18.0 mmol), *N,N′*-

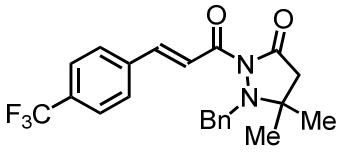
dicyclohexylcarbodiimide (4.10 g, 20 mmol) and dimethylaminopyridine (0.24 g, 2.0 mmol). The unpurified product was subjected to flash silica gel column chromatography (EtOAc:hexanes = 1:3) to afford **3.25d** as a yellow liquid (3.1 g, 65%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.67 (d, *J* = 15.6 Hz, 1H), 6.88 (dq, *J* = 13.8, 6.7 Hz, 1H), 3.01 (q, *J* = 7.1 Hz, 2H), 2.60 (s, 2H), 1.33 (s, 6H), 1.07 (t, *J* = 7.1 Hz, 3H); **^{19}F NMR (376 MHz, $CDCl_3$):** δ -65.20 (d, *J* = 6.8 Hz).



3.25e

1-Benzyl-2-cinnamoyl-5,5-dimethylpyrazolidin-3-one (3.25e)

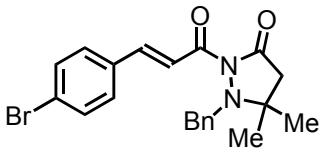
3.25e was prepared following **General Procedure A for Preparation of 2-Acryloylpyrazolidinone Derivatives** using cinnamic acid (2.67 g, 15.0 mmol), 1-benzyl-5,5-dimethylpyrazolidin-3-one (3.05 g, 15.0 mmol), *N,N′*-dicyclohexylcarbodiimide (3.30 g, 16.5 mmol) and dimethylaminopyridine (0.18 g, 1.5 mmol). The unpurified product was subjected to flash silica gel column chromatography (EtOAc:hexanes = 1:3) to afford **3.25e** as a yellow solid (3.0 g, 60%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.65 (d, *J* = 15.7 Hz, 1H), 7.52 (dd, *J* = 6.6, 2.9 Hz, 2H), 7.47 – 7.35 (m, 5H), 7.29 – 7.24 (m, 3H), 7.23 – 7.18 (m, 1H), 4.12 (s, 2H), 2.61 (s, 2H), 1.34 (s, 6H).



3.25f

(*E*)-1-Benzyl-5,5-dimethyl-2-(3-(4-(trifluoromethyl)phenyl)acryloyl)pyrazolidin-3-one (3.25f)

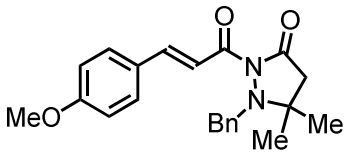
3.25f was prepared following **General Procedure A for Preparation of 2-Acryloylpyrazolidinone Derivatives** using (*E)*-3-(4-(trifluoromethyl)phenyl)acrylic acid (3.24 g, 15.0 mmol), 1-benzyl-5,5-dimethylpyrazolidin-3-one (3.05 g, 15.0 mmol), *N,N′*-dicyclohexylcarbodiimide (3.30 g, 16.5 mmol) and dimethylaminopyridine (0.18 g, 1.5 mmol). The unpurified product was subjected to flash silica gel column chromatography (EtOAc:hexanes = 1:3) to afford **3.25f** as a yellow solid (2.7 g, 45%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.66 – 7.54 (m, 5H), 7.50 – 7.42 (m, 1H), 7.40 (m, 2H), 7.28 – 7.23 (m, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 4.11 (s, 2H), 2.63 (s, 2H), 1.36 (s, 6H); **^{19}F NMR (470 MHz, $CDCl_3$):** δ -62.84.



3.25g

(*E*)-1-Benzyl-2-(3-(4-bromophenyl)acryloyl)-5,5-dimethylpyrazolidin-3-one (3.25g)

3.25g was prepared following **General Procedure A for Preparation of 2-Acryloylpyrazolidinone Derivatives** using (*E*)-3-(4-bromophenyl)acrylic acid (3.39 g, 15.0 mmol), 1-benzyl-5,5-dimethylpyrazolidin-3-one (3.05 g, 15.0 mmol), *N,N′*-dicyclohexylcarbodiimide (3.30 g, 16.5 mmol) and dimethylaminopyridine (0.18 g, 1.5 mmol). The unpurified product was subjected to flash silica gel column chromatography (EtOAc:hexanes = 1:3) to afford **3.25g** as a yellow solid (1.8 g, 29%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.57 – 7.46 (m, 3H), 7.42 – 7.35 (m, 5H), 7.26 – 7.16 (m, 3H), 4.11 (s, 2H), 2.61 (s, 2H), 1.35 (s, 6H).



3.25h

(*E*)-1-Benzyl-2-(3-(4-methoxyphenyl)acryloyl)-5,5-dimethylpyrazolidin-3-one (3.25h)

3.25h was prepared following **General Procedure A for Preparation of 2-Acryloylpyrazolidinone Derivatives** using (*E*)-3-(4-methoxyphenyl)acrylic acid (2.67 g, 15.0 mmol), 1-benzyl-5,5-dimethylpyrazolidin-3-one (3.05 g, 15.0 mmol), *N,N′*-dicyclohexylcarbodiimide (3.30 g, 16.5 mmol) and dimethylaminopyridine (0.18 g, 1.5 mmol). The unpurified product was subjected to flash silica gel column chromatography (EtOAc:hexanes = 1:3) to afford **3.25h** as a yellow solid (2.1 g, 38%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.63 (d, *J* = 15.7 Hz, 1H), 7.50 – 7.46 (m, 2H), 7.43 – 7.39 (m, 2H), 7.35 (d, *J* = 15.7 Hz, 1H), 7.28 – 7.24 (m, 2H), 7.22 – 7.17 (m, 1H), 6.91 – 6.87 (m, 2H), 4.12 (s, 2H), 3.84 (s, 3H), 2.58 (s, 2H), 1.32 (s, 6H).

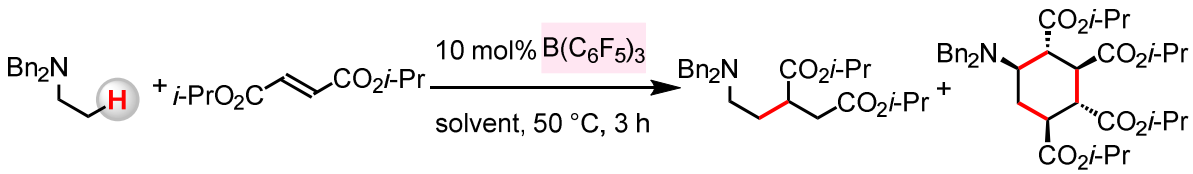
3.6.2.2. Optimization Studies for $(F_5C_6)_3B$-Catalyzed *β*-Alkylation involving *N*-Alkylamines

3.6.2.2.1. Evaluation of Reaction Conditions for $(F_5C_6)_3B$-Catalyzed *β*-Alkylation involving *N*-Alkylamines

Experimental Procedure for the Evaluation of Solvents (Table S3)

To a 15 mL oven-dried pressure vessel was added *N*,*N*-dibenzylethanamine **3.19a** (0.20 mmol), $B(C_6F_5)_3$ (10 mol%), diisopropyl fumarate **3.20a** (0.30 mmol), and solvent (0.20 mL) under a nitrogen atmosphere. The reaction mixture was placed in an oil bath at 50 °C and was allowed to stir for 3 hours. After the solution was cooled to 22 °C, it was concentrated *in vacuo*. The product yield was determined by the ^{1}H NMR analysis of the unpurified product mixtures using *m*-xylene as the internal standard.

Table S3. Evaluation of Solvents involving Amine **3.19a**



3.19a, 0.20 mmol **3.20a**, 0.30 mmol **3.21a** **3.22a**

entry	solvent	yield (%) **4d**	**5d**
1	*n*-hexane	75	22
2	toluene	71	21
3	DCM	70	27
4	TBME	60	27
5	Et_2O	52	36
6	THF	<5	<5

Conditions: *N*,*N*-dibenzylethanamine (**3.19a**, 0.20 mmol), diisopropyl fumarate (**3.20a**, 0.30 mmol), $B(C_6F_5)_3$ (10 mol%), solvent (0.20 mL), under N_2, 50 °C. The yield was determined by ^{1}H NMR analysis of unpurified reaction mixtures with *m*-xylene as the internal standard.

3.6.2.2.2. Effect of Concentration of Solution to Chemoselectivity of $(F_5C_6)_3B$-Catalyzed β-Alkylation involving Cyclic *N*-Alkylamines

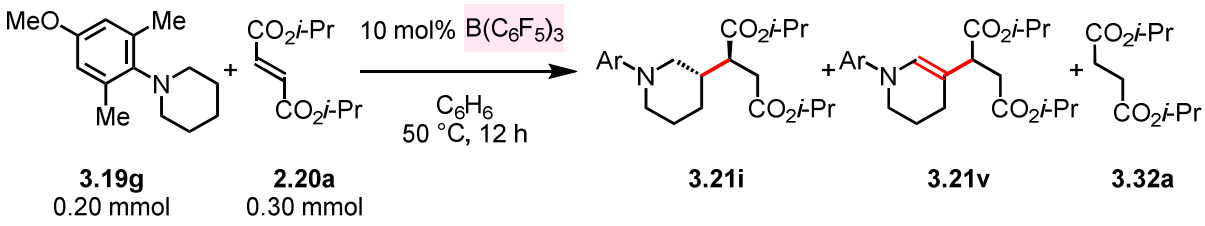
For piperidine substrates (e.g., *N*-arylpiperidine **3.19g**, Table S4) that react with **3.20a** to give a mixture of products in the forms of *N*-alkylamines (e.g., **3.21i**) and enamines (e.g., **3.21v**), we carried out a series of optimization studies that were aimed to selectively prepare **3.21i** (Table S4). Specifically, to a 15 mL oven-dried pressure vessel were added amine **3.19g** (0.20 mmol), $B(C_6F_5)_3$ (10 mol%), diisopropyl fumarate **3.25a** (0.30 mmol), and benzene (0.20 mL or 0.80 mL) under a nitrogen atmosphere. The reaction mixture was placed in an oil bath at 50 °C and was allowed to stir for 12 hours. Upon completion, the solution was cooled down to room temperature and was concentrated *in vacuo*. The yield values for **3.21i** and **3.21v** were determined by the ^{1}H NMR analysis of the unpurified product mixtures using *m*-xylene as the internal standard.

As shown in Table S4, it was found that, when the reaction was run in more dilute conditions (0.80 mL, 0.25 M in benzene) than the standard reaction conditions (0.20 mL, 1.0 M in benzene), the *N*-alkylamine product **3.21i** can be obtained more preferably over enamine **3.21v**.

Furthermore, when the enamine product (e.g., **3.21v**) is generated, the formation of diisopropyl succinate (**3.32a**) was observed. This is likely due to the hydrogenation of **3.20a** by *in situ* generated borohydride and ammonium ion to regenerate the Lewis acid and Brønsted base catalysts. We hypothesized that if a larger quantity of **3.20a** is present in the reaction mixture to serve as a sacrificial H^+/H^- acceptor, the formation of enamine product would be favored.

To a 15 mL oven-dried pressure vessel was added 1-(4-methoxy-2,6-dimethylphenyl)-4,4-dimethylpiperidine **3.19h** (0.2 mmol), $B(C_6F_5)_3$ (10 mol%), diisopropyl fumarate **3.20a** (0.3 mmol, 1.5 equiv.) and DCM (0.1 mL) under a nitrogen atmosphere (Scheme S1). The reaction mixture was placed in an oil bath at 50 °C and was allowed to stir for 12 hours. After the solution was

Table S4. Evaluation of Solvent Concentration involving Amine **3.19g**



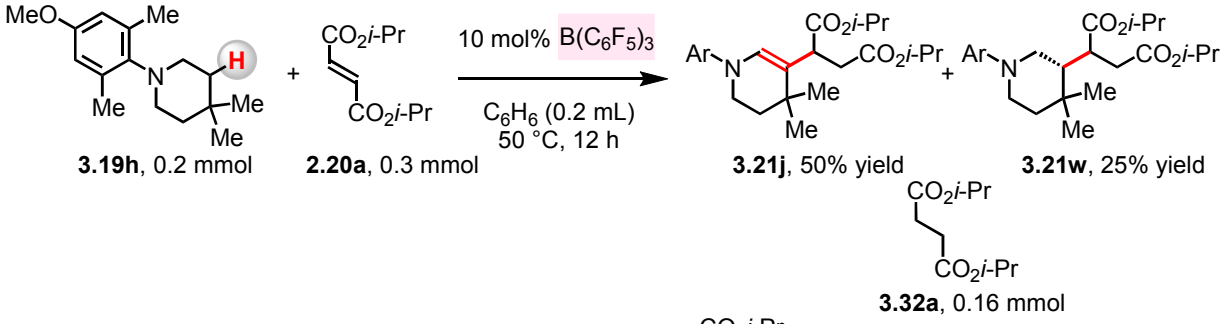
3.19g 0.20 mmol | **2.20a** 0.30 mmol | **3.21i** | **3.21v** | **3.32a**

entry	solvent (mL)	yield		
		3.21i (%)	**3.21v** (%)	**3.32a** (mmol)
1	C_6H_6 (0.20 mL)	58	29	0.07
2	C_6H_6 (0.80 mL)	89	<5	0.02

Conditions: 1-(4-methoxy-2,6-dimethylphenyl)piperidine (**3.19g**, 0.20 mmol), diisopropyl fumarate (**2.20a**, 0.30 mmol), $B(C_6F_5)_3$ (10 mol%), solvent, under N_2, 50 °C. The yield was determined by ^1H NMR analysis of unpurified reaction mixtures with *m*-xylene as the internal standard.

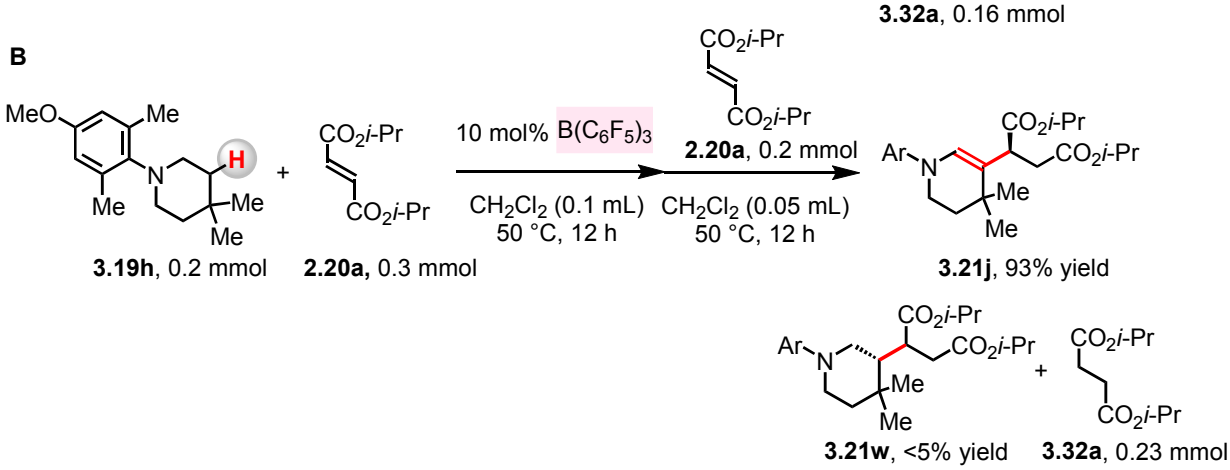
Scheme S1. Evaluation of Reaction Conditions involving Amine **3.19h**

A



3.19h, 0.2 mmol | **2.20a**, 0.3 mmol | **3.21j**, 50% yield | **3.21w**, 25% yield | **3.32a**, 0.16 mmol

B



3.19h, 0.2 mmol | **2.20a,** 0.3 mmol | **3.21j**, 93% yield | **3.21w**, <5% yield | **3.32a**, 0.23 mmol

cooled to 22 °C, diisopropyl fumarate **2.20a** (0.2 mmol, 1.0 equiv.) and DCM (0.05 mL) were added under a nitrogen atmosphere. Then the reaction mixture was placed again in an oil bath at 50 °C and was allowed to stir for 12 hours. Upon completion, the solution was cooled to 22 °C and was concentrated *in vacuo*. The product yield was determined by the ^{1}H NMR analysis of the unpurified product mixtures using *m*-xylene as the internal standard. It was found that adding 2.5 equiv. of **2.20a** in a batchwise manner improves the product yield as well as the chemoselectivity of the reaction to yield enamine product **3.21j** (Scheme S1B).

3.6.2.3. Optimization Studies for Diastereoselective β-Alkylation

Experimental Procedure for the Optimization of Diastereoselective Reaction (Table 3.4)

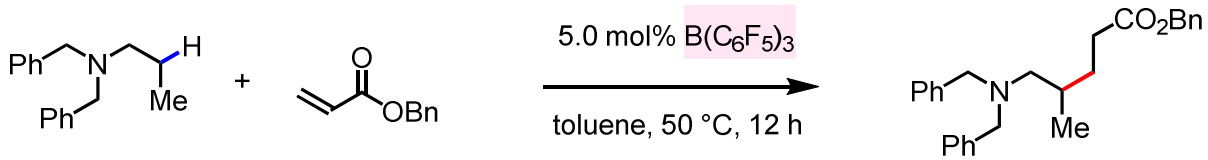
To a 15 mL oven-dried pressure vessel were added (*R*)-1-benzyl-2-(((*tert*-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine **3.19o** (0.10 mmol), **3.23** (0.15 mmol), $B(C_6F_5)_3$ (10 mol%), Lewis acid co-catalyst (10 mol%), HBPin (0 mol% or 70 mol%), and benzene (0.60 mL) under a nitrogen atmosphere. The reaction mixture was placed in an oil bath at 60 °C and was allowed to stir for 24 or 36 hours. Upon completion, the solution was cooled to 22 °C and concentrated *in vacuo*. The product yield and dr were determined by the ^{1}H NMR and ^{19}F NMR analyses of the unpurified product mixtures using mesitylene (for ^{1}H NMR analysis) and perfluorobenzene (for ^{19}F NMR analysis) as the internal standard.

3.6.2.4. Studies for Enantioselective *β*-Alkylation with a Chiral Boron Lewis Acid Catalyst

Based on the hypothesis that $B(C_6F_5)_3$ is responsible for the activation of both the *N*-alkylamine and *α*,*β*-unsaturated compounds, we envisioned the use of chiral boron Lewis acid catalyst to achieve the enantioselective *β*-alkylation reaction.

N,*N*-dibenzylpropan-1-amine (**3.19b**) and benzyl acrylate (**3.20c**) were used as model substrates which afforded *β*-alkylated product **3.21x** in 75% yield (Scheme S2). We first examined the ability of a chiral borane catalyst to promote the C–C bond forming reaction in an enantioselective manner. No desired product was observed using less Lewis acidic Du's catalyst (Scheme S3A).[22] When Du's catalyst was used in combination with $B(C_6F_5)_3$, the product was obtained in 70% yield and 50:50 er (Scheme S3B).

Scheme S2. *β*-Amino C–H Alkylation Involving **3.19b** and **3.20c**



3.19b, 0.10 mmol **3.20c**, 0.15 mmol **3.21x**, 75% yield

Benzyl 5-(dibenzylamino)-4-methylpentanoate (3.21x)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, *J* = 5.4 Hz, 9H), 7.28 (t, *J* = 7.5 Hz, 4H), 7.20 (t, *J* = 7.3 Hz, 2H), 5.10 (s, 2H), 3.48 (s, 4H), 2.33 – 2.25 (m, 2H), 2.23 (dd, *J* = 12.4, 7.3 Hz, 1H), 2.14 (dd, *J* = 12.5, 7.3 Hz, 1H), 1.86 – 1.79 (m, 1H), 1.79 – 1.71 (m, 1H), 1.40 – 1.31 (m, 1H), 0.84 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.8, 139.8, 136.1, 128.9, 128.5, 128.2, 128.14, 128.10, 126.7, 66.1, 60.3, 58.8, 31.7, 30.4, 29.7, 17.8; **IR** (neat) ν 2951, 2926, 1733, 1493, 1452, 1256, 1167, 746, 697 cm^{-1}; **HRMS** (DART) Calcd for $C_{27}H_{32}NO_2$ (MH^+): 402.2428; found: 402.2427.

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Acq. Instrument : Wasa_LC1                         Location :   71
Injection Date  : 1/21/2019 2:29:06 PM                 Inj :   1
                                                 Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2019-01-21 12-26-09\column3 1.5% IPA 98.5% hex 60min-0
                  .3ml.M (Sequence Method)
Last changed    : 1/21/2019 12:26:09 PM by SYSTEM
Additional Info : Peak(s) manually integrated
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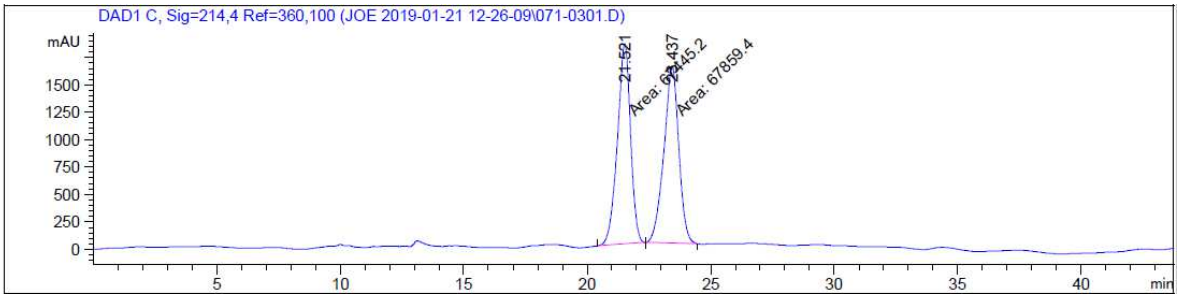


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Signal 3: DAD1 C, Sig=214,4 Ref=360,100

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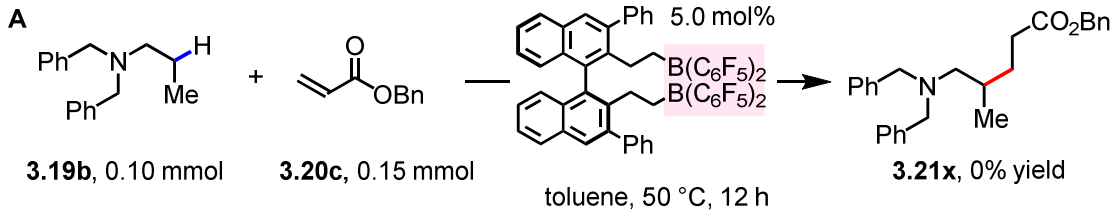
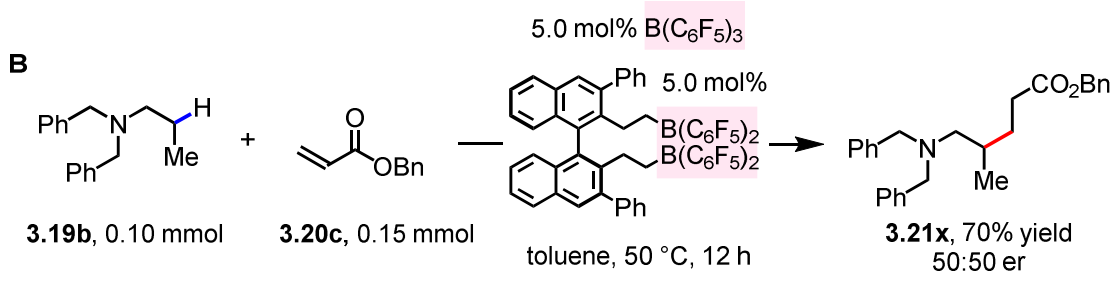
Scheme S3. Evaluation of Du's Catalyst





Experimental Procedure for the Evaluation of Du's Catalyst

An oven-dried sealed tube equipped with a magnetic stir bar was used. To this tube were added

(*S*)-3,3'-diphenyl-2,2'-divinyl-1,1'-binaphthalene (0.005 mmol), $HB(C_6F_5)_2$ (0.01 mmol), and toluene (0.2 mL) under nitrogen atmosphere.[22] This reaction mixture was allowed to stir for 20 minutes at 22 °C to generate the chiral organoborane catalyst. To this mixture were added **3.19b** (0.10 mmol), **3.20c**[27] (0.15 mmol), $B(C_6F_5)_3$ (0.005 mmol), and toluene (0.2 mL). The reaction mixture was placed in an oil bath at 50 °C and was allowed to stir for 12 hours. Upon completion, the reaction mixture was concentrated *in vacuo*. The product yield was determined by the ^{1}H NMR analysis of the unpurified product mixtures using mesitylene as the internal standard. The product was isolated and purified using preparatory TLC. The er was determined by HPLC analysis of the isolated and purified product. **HPLC** (Chiralcel OD-H; 1.5%/ 98.5% isopropanol/ hexanes, 0.3 mL/min; tr = 22.0 min, 24.0 min; 50:50 er).

```
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Acq. Instrument : Wasa_LC1                         Location :   75
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                                                  Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2019-01-24 12-08-54\column3 1.5% IPA 98.5% hex 40min-0
                  .3ml.M (Sequence Method)
Last changed    : 1/24/2019 12:08:54 PM by SYSTEM
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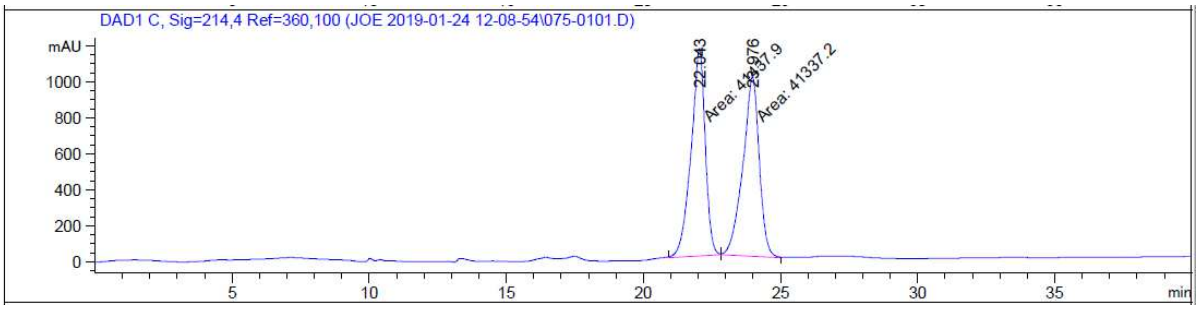


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Peak RetTime Type  Width     Area      Height     Area
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   1  22.043 MM    0.6005 4.14379e4  1150.06067  50.0608
   2  23.976 MM    0.6922 4.13372e4   995.28009  49.9392
```

[27] Liu, Y.; Du, H. *J. Am. Chem. Soc*. **2013**, *135*, 6810–6813.

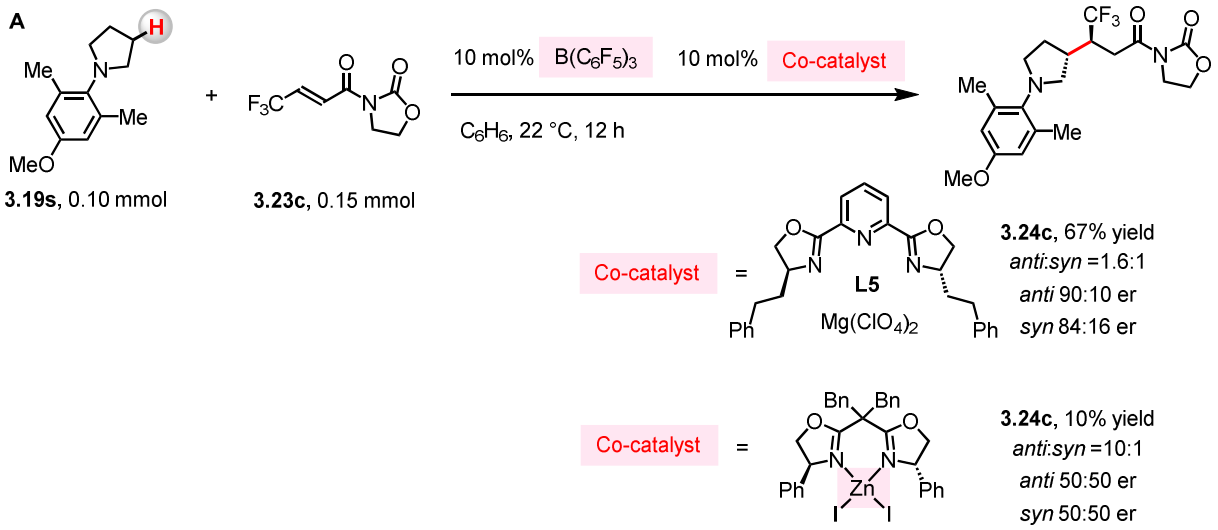
3.6.2.5. Evaluation of Various Auxiliaries and Chiral Lewis Acid Co-Catalysts for Enantioselective β-Amino C–H Alkylation

To achieve highly enantioselective β-alkylation of *N*-alkylamines, various combinations of chiral Lewis acid co-catalysts and electrophiles containing different auxiliaries were evaluated (Scheme S4).

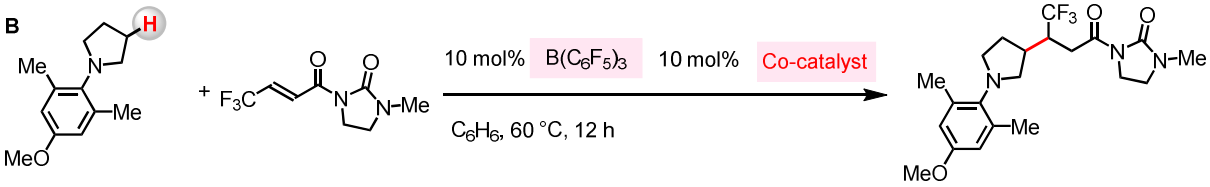
Using achiral substrates *N*-arylpyrrolidine **3.19s** and oxazolidinone-substituted **3.23c**, we evaluated various chiral organometallic complexes to find that $Mg(ClO_4)_2$/**L5** give **3.24c** with 67% yield in up to 90:10 er. In comparison, when a chiral Zn-BOX complex was used, **3.24c** was produced in 10 % yield (10:1 dr, 50:50 er; Scheme S4A).

In order to identify the optimal auxiliary, we evaluated substrates **3.24d**, **3.24e** and **3.24f** in the presence of various chiral organometallic co-catalysts. However, the desired products were obtained in 0–30% yield and up to 69:31 er (Schemes S4B–D).

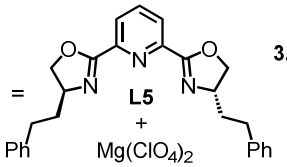
Scheme S4. Evaluation of Different Electrophiles and Chiral Lewis Acid Co-Catalysts



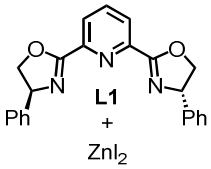
B



3.23s, 0.10 mmol **3.23d**, 0.15 mmol

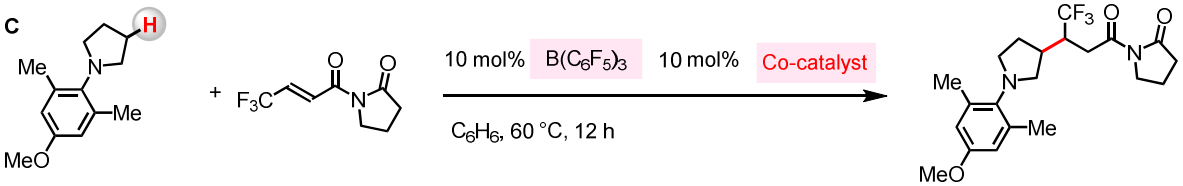
Co-catalyst =  **L5** + $Mg(ClO_4)_2$

3.24d, 30% yield
1.0:1 dr
69:31 er

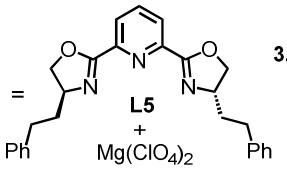
Co-catalyst =  **L1** + ZnI_2

3.24d, 0% yield

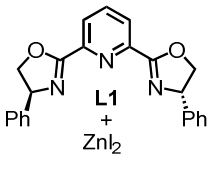
C



3.19s, 0.10 mmol **3.23e**, 0.15 mmol

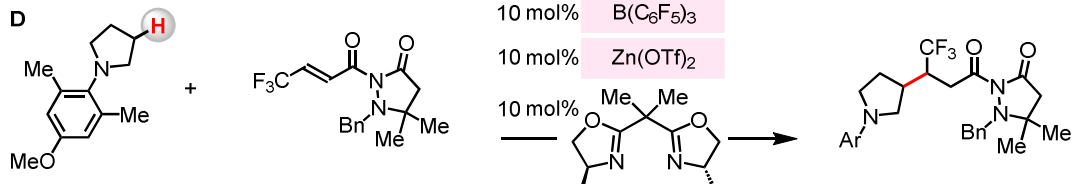
Co-catalyst =  **L5** + $Mg(ClO_4)_2$

3.24e, 0% yield

Co-catalyst =  **L1** + ZnI_2

3.24e, 0% yield

D



3.19s, 0.10 mmol **3.23e**, 0.15 mmol

3.24e, 0% yield

3.6.2.6. Optimization Studies for Enantioselective β-Alkylation Involving 3.23c with Chiral Mg-based Complexes

Experimental Procedure for the Optimization of Ligand (Table 3.5)

To a 15 mL oven-dried pressure vessel was added $Mg(ClO_4)_2$ (0.010 mmol, 10 mol%), **ligand** (0.010 mmol, 10 mol%), benzene (0.3 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C. Subsequently, 1-(4-methoxy-2,6-dimethylphenyl)pyrrolidine **3.19s** (0.10 mmol), (*E*)-3-(4,4,4-trifluorobut-2-enoyl)oxazolidin-2-one **3.23c** (0.15 mmol), and benzene (0.30 mL) were added to the vial under nitrogen atmosphere, and the resulting mixture was allowed to stir at 22 °C for 12 h. Upon completion, the reaction mixture was concentrated *in vacuo*. The product yield and dr were determined by the ^{1}H NMR and ^{19}F NMR analyses of the unpurified product mixtures using mesitylene (for ^{1}H NMR analysis) and perfluorobenzene (for ^{19}F NMR analysis) as the internal standard. The product was purified by preparative TLC (EtOAc:hexanes = 1:3). The er values of product **3.23c** was determined by HPLC analysis of the isolated and purified product.

3.6.2.7. Optimization Studies for Enantioselective β-Alkylation Involving 3.25a with Chiral Lewis Acid Co-Catalysts

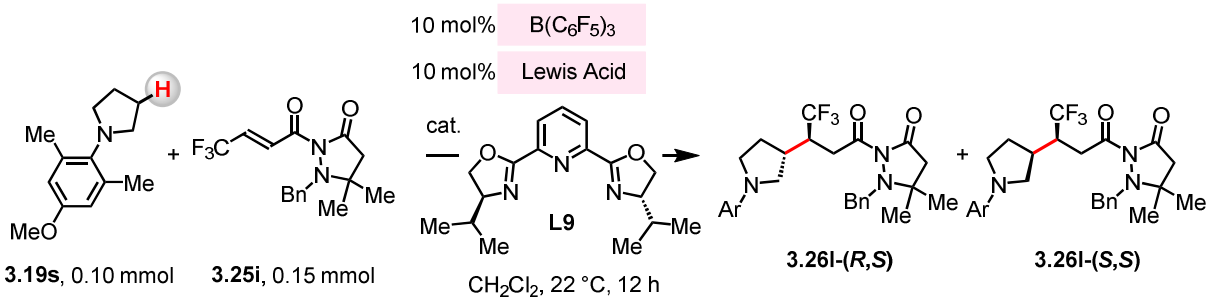
Experimental Procedure for the Optimization of Lewis Acid Co-Catalyst (Table S5)

To a 15 mL oven-dried pressure vessel was added Lewis Acid (0.010 mmol, 10 mol%), 2,6-bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)pyridine **L9** (0.012 mmol, 12 mol%), and DCM (0.50 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 min at 22 °C. Subsequently, (*E*)-1-benzyl-5,5-dimethyl-2-(4,4,4-trifluorobut-2-enoyl)pyrazolidin-3-one **3.25i** (0.15 mmol), 1-(4-methoxy-2,6-dimethylphenyl)pyrrolidine **3.19s** (0.10 mmol), $B(C_6F_5)_3$ (0.010 mmol, 10 mol%) and DCM (0.50 mL) were added to the reaction vessel, and the resulting mixture was allowed to stir at 22 °C for 12 hours. Upon completion, the solution was concentrated *in vacuo*. The product yield and dr were determined by the ^{1}H NMR and ^{19}F NMR analyses of the unpurified product mixtures using mesitylene (for ^{1}H NMR analysis) and perfluorobenzene (for ^{19}F NMR analysis) as the internal standard. The product was purified by preparative TLC (EtOAc:hexanes = 1:3). The er values of product **3.26l** was determined by HPLC analysis of the isolated and purified product.

Experiments for Evaluation of *N*-Aryl Substituents

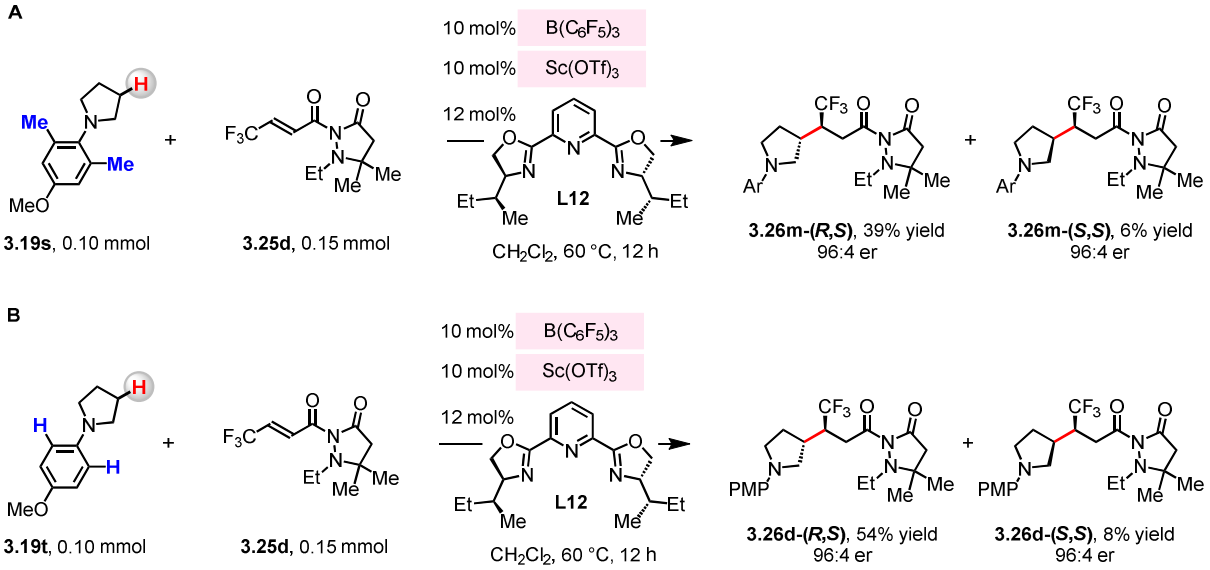
We evaluated *N*-arylpyrrolidine with different substituents on the aromatic ring (e.g., **3.16s**, **3.19t**) in the presence of $B(C_6F_5)_3$ and **L12**−$Sc(OTf)_3$ (Scheme S5). The reaction between **3.19s** and **3.25d** gave **3.26m** in 45% yield (6.5:1 dr, 96:4 er). When less sterically hindered *p*-methoxyphenyl (PMP)-substituted **3.19t** unit was reacted with **3.25d**, **3.26d** could be produced in 62% yield, 6.7:1 dr, and 96:4 er.

Table S5. Optimization of Chiral Lewis Acid Co-Catalyst



entry	Lewis Acid	yield (%) and er	
		3.26l-(*R*,*S*)	**3.26l-(*S*,*S*)**
1	$La(OTf)_3$	49, (50:50 er)	18, (50:50 er)
2	$Sm(OTf)_3$	38, (50:50 er)	11, (50:50 er)
3	$Eu(OTf)_3$	0	0
4	$Yb(OTf)_3$	0	0
5	$Sc(OTf)_3$	26, (96:4 er)	17, (96:4 er)

Scheme S5. Evaluation of *N*-Aryl Substituents

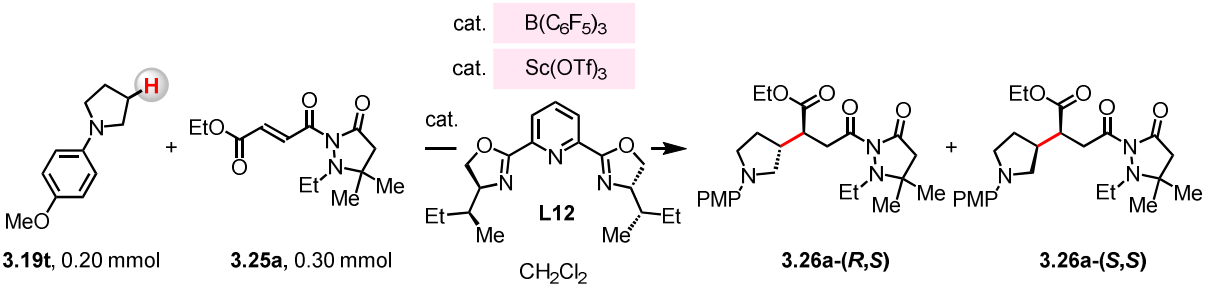


3.6.2.8. Optimization Studies for Enantioselective β-Alkylation Involving 6c with Chiral Sc-based Complexes

3.6.2.8.1. Evaluation of Reaction Parameters (Table S6)

To a 15 mL oven-dried pressure vessel was added $Sc(OTf)_3$ (0.020 mmol, 10 mol%), 2,6-bis((*S*)-4-((*S*)-sec-butyl)-4,5-dihydrooxazol-2-yl)pyridine **L12** (0.024 mmol, 12 mol%), and DCM (1.0 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 min at 22 °C. Subsequently, ethyl (*E*)-4-(2-ethyl-3,3-dimethyl-5-oxopyrazolidin-1-yl)-4-oxobut-2-enoate **3.25a** (0.30 mmol), 1-(4-methoxyphenyl)pyrrolidine **3.19t** (0.20 mmol), $B(C_6F_5)_3$ (0.020 mmol, 10 mol%) and DCM (1.0 mL) were added to the reaction vessel, and the resulting mixture was placed in an oil bath at 60 °C and was allowed to stir for 1 hour or 3 hours. Upon completion, the solution was cooled to 22 °C and concentrated *in vacuo*. The product yield and dr were determined by the ^{1}H NMR analyses of the unpurified product mixtures using as the internal standard. The product was purified by preparative TLC (EtOAc:hexanes = 1:1). The er values of product **3.26a** was determined by HPLC analysis of the isolated and purified product.

Table S6. Optimization of Reaction Parameters



entry	$B(C_6F_5)_3$ (mol%)	$Sc(OTf)_3$/**L12** (mol%)	time (h)	temperature (°C)	yield (%) and er **3.26a-(*R*,*S*)**	**3.26a-(*S*,*S*)**
1	10	0	3	60	0	0
2	0	10	3	60	0	0
3	10	10	3	60	51, (97:3 er)	33, (98:2 er)
4	10	10	3	22	46, (97:3 er)	24, (98:2 er)
5	10	10	1	60	56, (97:3 er)	29, (98:2 er)
6	10	5	1	60	55, (97:3 er)	30, (98:2 er)
7	5	5	1	60	32, (97:3 er)	18, (98:2 er)

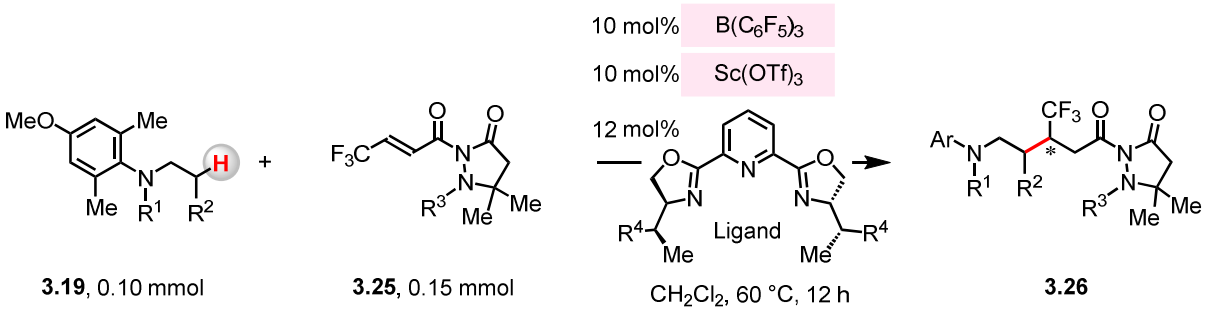
3.6.2.8.2. General Reaction Procedure for Evaluation of Chiral Ligands (See Table 3.6)

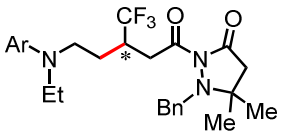
To a 15 mL oven-dried pressure vessel was added $Sc(OTf)_3$ (0.010 mmol, 5.0 mol%), **Ligand** (0.012 mmol, 6.0 mol%), and DCM (1.0 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 min at 22 °C. Subsequently, ethyl (*E*)-4-(2-ethyl-3,3-dimethyl-5-oxopyrazolidin-1-yl)-4-oxobut-2-enoate **3.25a** (0.30 mmol), 1-(4-methoxyphenyl)pyrrolidine **3.19t** (0.20 mmol), $B(C_6F_5)_3$ (0.020 mmol, 10 mol%) and DCM (1.0 mL) were added to the reaction vessel, and the resulting mixture was placed in an oil bath at 60 °C and was allowed to stir for 1 hour. Upon completion, the solution was cooled to 22 °C and concentrated *in vacuo*. The product yield and dr were determined by the ^1H NMR analyses of the unpurified product mixtures using mesitylene as the internal standard. The product was purified by preparative TLC (EtOAc:hexanes = 1:1). The er values of product **3.26a** was determined by HPLC analysis of the isolated and purified product.

3.6.2.9. Evaluation of Acyclic Amine Substrates for Enantioselective β-Alkylation with Chiral Sc-based Complexes

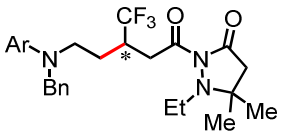
We have evaluated several acyclic amines (**3.19**) for enantioselective β-amino C–H alkylation; however, the current conditions were found to be incompatible with this class of substrate (Scheme S6).

Scheme S6. Evaluation of Acyclic Amine Substrates

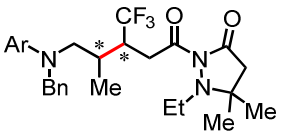




3.26n, 10% yield[b]



3.26o, <5% yield[c]

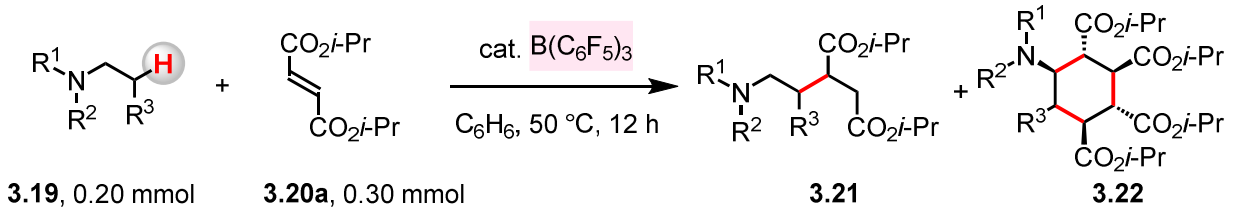


3.26p, <5% yield[c]

[a]Conditions: amine (**3.19**, 0.10 mmol), α,β-unsaturated compound (**3.25**, 0.15 mmol), $B(C_6F_5)_3$ (10 mol%), $Sc(OTf)_3$(10 mol%), ligand (12 mol%), CH_2Cl_2 (1.0 mL), under N_2, 60 °C.[b] **L9** (R^4=Me) was used as ligand. [c] **L12** (R^4=Et) was used as ligand.

3.6.2.10. General Procedures for β-Alkylation of *N*-Alkylamines

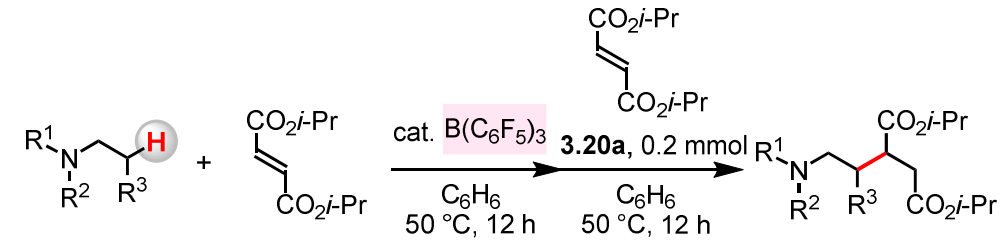
General Procedure C for the β-Alkylation of *N*-Alkylamines (See Tables 3.1-3.3 in the Manuscript)



3.19, 0.20 mmol **3.20a**, 0.30 mmol **3.21** **3.22**

To a 15 mL oven-dried pressure vessel was added amine (0.20 mmol), $B(C_6F_5)_3$ (5.0 or 10 mol%), α,β-unsaturated compound (0.30 mmol, 1.5 equiv.) and benzene under a nitrogen atmosphere. The reaction mixture was placed in an oil bath at 50 °C and was allowed to stir for 12 hours. Upon completion, the solution was cooled to 22 °C and concentrated *in vacuo* followed by flash silica gel column chromatography.

General Procedure D for the β-Alkylation of *N*-Alkylamines (See Tables 3.2-3.3 in the Manuscript)

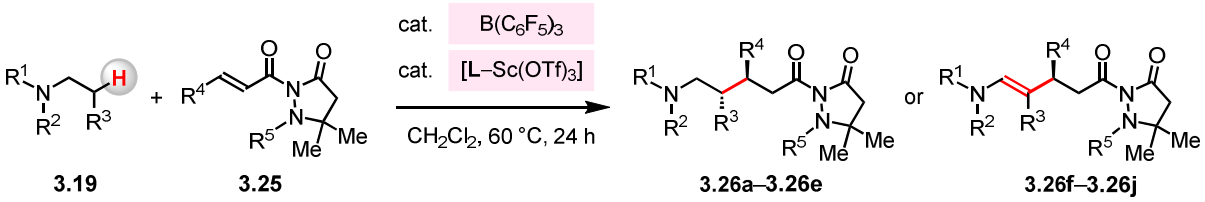


3.19, 0.20 mmol **3.20a**, 0.30 mmol **3.21**

To a 15 mL oven-dried pressure vessel was added amine (0.20 mmol), $B(C_6F_5)_3$ (5.0 or 10 mol%), α,β-unsaturated compound (0.30 mmol, 1.5 equiv.) and benzene (0.30 mL) under a nitrogen atmosphere. The reaction mixture was placed in an oil bath at 50 °C and was allowed to stir for 12 hours. After the solution was cooled to 22 °C, α,β-unsaturated compound (0.20 mmol, 1.0 equiv.)

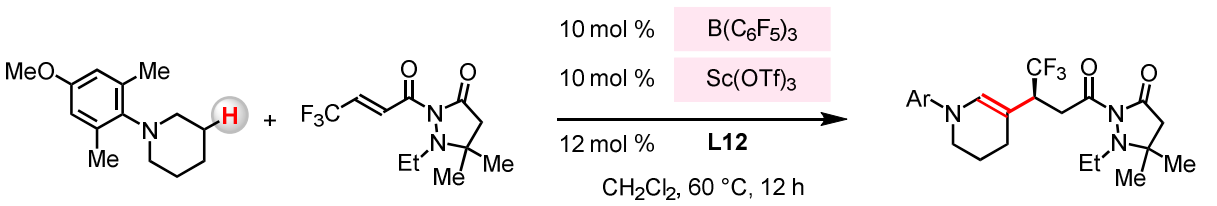
and benzene (0.10 mL) were added under a nitrogen atmosphere and the reaction mixture was again placed in an oil bath at 50 °C and was allowed to stir for 12 hours. Upon completion, the solution was cooled to 22 °C and concentrated *in vacuo* followed by flash silica gel column chromatography.

General Procedure E for the Enantioselective *β*-Alkylation of *N*-Alkylamines (See Tables 3.6-3.7 in the Manuscript)



To a 15 mL oven-dried pressure vessel was added $Sc(OTf)_3$ (5.0 or 10 mol%), **ligand** (6.0 or 12 mol%), and DCM (0.50 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 min at 22 °C. Subsequently, *α,β*-unsaturated compound **3.25** (0.15 or 0.20 mmol), amine **3.19** (0.10 mmol), $B(C_6F_5)_3$ (10 or 20 mol%) and DCM (0.50 mL) were added to the reaction vessel, and the resulting mixture was placed in an oil bath at 60 °C or 80 °C and was allowed to stir for 1–36 hours. Upon completion, the solution was cooled to 22 °C and concentrated *in vacuo* followed by flash silica gel column chromatography.

Procedure for Large Scale Reaction



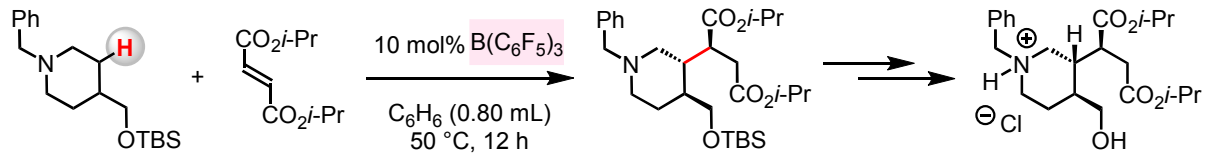
3.19g, 4.0 mmol **3.25d**, 8.0 mmol **3.26f**, >95% yield, 1.9 g, 95:5 er

To a 25 mL oven-dried sealed tube was added $Sc(OTf)_3$ (10 mol%), 2,6-bis((*S*)-4-((*S*)-sec-butyl)-4,5-dihydrooxazol-2-yl)pyridine **L12** (12 mol%), and DCM (5.0 mL) under nitrogen atmosphere. The mixture was allowed to stir for 2 hours at 22 °C. Subsequently, (*E*)-1-ethyl-5,5-dimethyl-2-(4,4,4-trifluorobut-2-enoyl)pyrazolidin-3-one **3.25d** (8.0 mmol), 1-(4-methoxy-2,6-dimethylphenyl)piperidine **3.19g** (4.0 mmol), $B(C_6F_5)_3$ (10 mol%) and DCM (1.0 mL) were added to the reaction vessel, and the resulting mixture was placed in an oil bath at 60 °C and was allowed to stir for 12 hours. Upon completion, the solvent was cooled to 22 °C and concentrated *in vacuo* followed by purification through flash silica gel column chromatography to afford the product as a light yellow oil (1.93 g, 95% yield, 95:5 er). The er value was determined by HPLC analysis of the isolated and purified product.

3.6.3. Determination of Relative Configuration

3.6.3.1. Determination of the Relative Configuration of 3.21e-Major

The relative configurations of **3.21e-major** was determined by the X-ray crystallographic analysis of **3.34e-major**, which was derived from **3.21e-major** (Scheme S7).



3.19d, 0.20 mmol **3.20a**, 0.30 mmol — **3.21e**, 74% yield, 1.1:1 dr — **3.34e-major**

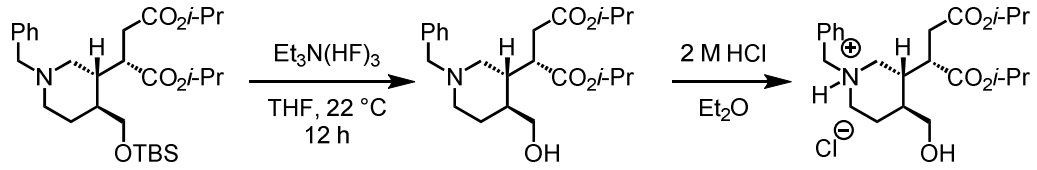
Diisopropyl 2-(1-benzyl-4-(((*tert*-butyldimethylsilyl)oxy)methyl)piperidin-3-yl)succinate (3.21e)

1-Benzyl-4-(((*tert*-butyldimethylsilyl)oxy)methyl)piperidine **3.19d** was reacted with diisopropyl fumarate **3.20a** following the **General Procedure C** using $B(C_6F_5)_3$ (10 mol%) as the Lewis acid catalyst and benzene (0.80 mL) as the solvent. ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was 1.1:1. After purification by flash silica gel column chromatography (ethyl ether:hexanes = 1:4), **3.21e** was obtained as a mixture of diastereomers (77.0 mg, 74%). Further purification was carried out by PTLC using ethyl ether:DCM = 1:6 as the eluent to separate **3.21e-major** and **3.21e-minor**. The relative configuration for **3.21e-major** and **3.21e-minor** were assigned based on X-ray crystallography data of **3.34e-major** and **3.34e-minor**, respectively (see **Section 3.6.10**).

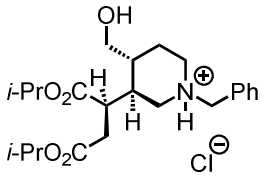
3.21e-Major. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (dp, *J* = 22.0, 7.5 Hz, 5H), 4.98 (dp, *J* = 16.3, 6.4 Hz, 2H), 3.71 (dd, *J* = 10.0, 2.6 Hz, 1H), 3.65 (dd, *J* = 10.1, 5.1 Hz, 1H), 3.52 (d, *J* = 13.4 Hz, 1H), 3.41 (d, *J* = 13.4 Hz, 1H), 3.09 (dt, *J* = 11.2, 3.4 Hz, 1H), 2.82 (tt, *J* = 16.1, 10.8 Hz, 3H), 2.22 (dd, *J* = 16.7, 3.7 Hz, 1H), 1.85 (t, *J* = 11.2 Hz, 1H), 1.82 – 1.77 (m, 1H), 1.76 – 1.63 (m,

2H), 1.46 (pt, J = 11.9, 6.7 Hz, 2H), 1.21 (dt, J = 12.1, 6.0 Hz, 12H), 0.87 (d, J = 3.2 Hz, 9H), 0.03 (d, J = 2.9 Hz, 6H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 172.7, 171.6, 138.2, 129.1, 129.0, 128.2, 128.1, 126.9, 67.91, 67.86, 64.6, 63.3, 55.4, 53.3, 40.7, 40.4, 40.0, 35.3, 29.3, 26.0, 25.9, 21.9, 21.82, 21.80, 21.75, 18.3, -5.4, -5.5; **IR (neat):** ν 2950, 2854, 1727, 1466, 1372, 1254, 1173, 1104, 834, 775 cm^{-1}; **HRMS (DART):** Calcd for $C_{29}H_{50}NO_5Si$ (MH^+): 520.3453; found: 520.3454.

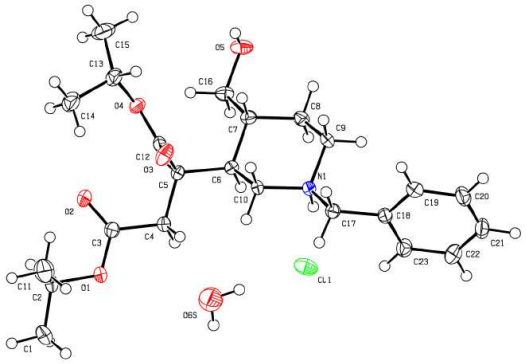
Scheme S7. Derivatization of **3.21e-Major** and Crystal Structure of **3.34e-Major**



3.21e-major | **3.34e-major-int** 97% yield | **3.34e-major**



3.34e-major ≡



1-Benzyl-3-(1,4-diisopropoxy-1,4-dioxobutan-2-yl)-4-(hydroxymethyl)piperidin-1-ium chloride (3.34e-major)

3.34e-Major was synthesized by the following procedure. To a solution of **3.21e-major** (386 mg, 0.75 mmol) in THF (10 mL) was added $Et_3N(HF)_3$ (0.50 mL) in a dropwise manner. The reaction was allowed to stir at 22 °C for 12 hours. The reaction mixture was concentrated and filtered through a plug of Celite using DCM as solvent. The unpurified product was then subjected to flash silica gel column chromatography (EtOAc:hexanes = 9:1) to afford diisopropyl 2-(1-benzyl-4-(hydroxymethyl)piperidin-3-yl)succinate **3.34e-major-int** as a colorless oil (295 mg, 97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.20 (m, 5H), 5.01 (dp, J = 9.8, 6.2 Hz, 2H), 3.83 (dd, J =

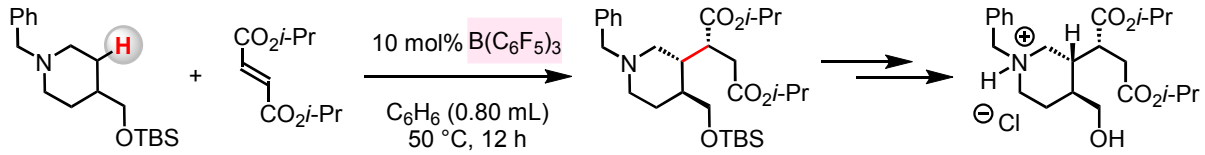
11.5, 4.1 Hz, 1H), 3.64 (dd, *J* = 11.5, 3.2 Hz, 1H), 3.55 (d, *J* = 13.2 Hz, 1H), 3.43 (d, *J* = 13.2 Hz, 1H), 3.18 (td, *J* = 6.3, 3.3 Hz, 1H), 2.98 – 2.83 (m, 2H), 2.76 (dd, *J* = 17.3, 8.2 Hz, 1H), 2.37 (dd, *J* = 17.3, 6.3 Hz, 1H), 2.23 (s, 1H), 1.94 – 1.82 (m, 2H), 1.72 (t, *J* = 11.1 Hz, 1H), 1.63 (dd, *J* = 10.2, 3.9 Hz, 2H), 1.60 – 1.46 (m, 2H), 1.30 – 1.18 (m, 14H).

3.34e-Major-int was then diluted in ethyl ether (0.10 mL) and 2.0 M HCl in ethyl ether was added dropwise to the solution until a white precipitate was formed. The solid was allowed to precipitate out of solution, whereupon the solvent was removed *in vacuo* to afford **3.34e-major** as a white solid.

3.34e-Major was recrystallized using the vapor-vapor diffusion method, using *i*-PrOH to dissolve the product in an inner vial, and ethyl ether as the precipitant placed in the outer vial in order for slow diffusion to occur into the inner vial. The solution was cooled to 0 °C, whereupon a crystal was obtained for X-ray crystallography. The X-ray crystallographic analysis revealed that the relative configuration of **3.34e-major** is (*R,R,R*) or (*S,S,S*). The relative configuration of products **3.21e-major**, **3.21i-major**, and **3.21t-major** were assigned in analogy.

3.6.3.2. Determination of the Relative Configuration of 3.21e-Minor

The relative configurations of **3.21e-Minor** was determined by the X-ray crystallographic analysis of **3.34e-minor**, which was derived from **3.34e-minor** (Scheme S8).



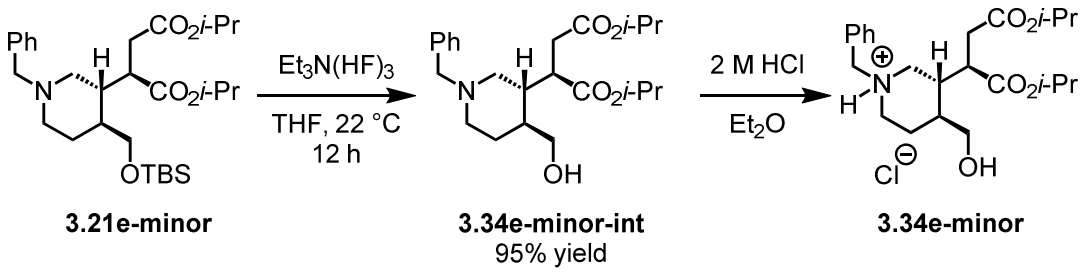
3.19d, 0.20 mmol **3.20a**, 0.30 mmol

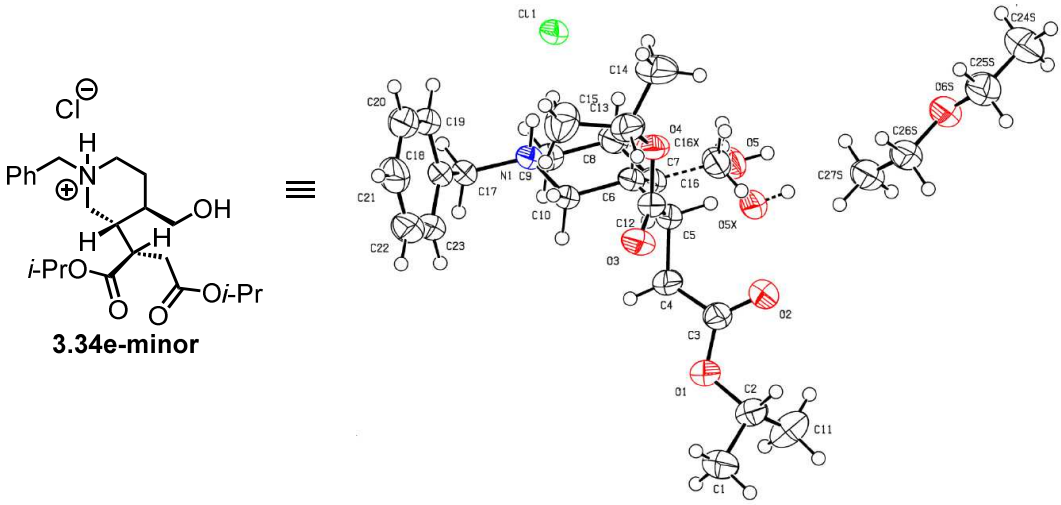
3.21e, 74% yield
1.1:1 dr

3.34e-minor

3.21e-Minor. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.23 (m, 4H), 7.23 – 7.17 (m, 1H), 5.03 – 4.93 (m, 1H), 4.93 – 4.84 (m, 1H), 3.61 (dd, *J* = 10.3, 4.1 Hz, 1H), 3.55 (t, *J* = 5.2 Hz, 1H), 3.50 (d, *J* = 13.2 Hz, 1H), 3.36 (d, *J* = 13.2 Hz, 1H), 3.19 (dt, *J* = 12.2, 3.6 Hz, 1H), 2.86 (d, *J* = 11.2 Hz, 1H), 2.67 – 2.50 (m, 2H), 2.35 – 2.24 (m, 1H), 2.09 (d, *J* = 11.0 Hz, 1H), 1.95 (t, *J* = 11.5 Hz, 1H), 1.78 – 1.65 (m, 2H), 1.54 (tt, *J* = 14.2, 7.1 Hz, 1H), 1.33 (dq, *J* = 11.0, 5.3 Hz, 1H), 1.20 (dd, *J* = 10.0, 6.3 Hz, 6H), 1.13 (d, *J* = 6.3 Hz, 3H), 1.03 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.04 (d, *J* = 5.8 Hz, 6H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 173.7, 172.0, 138.3, 129.0, 128.1, 126.9, 125.5, 67.9, 67.8, 65.0, 63.3, 54.4, 53.9, 41.3, 39.8, 39.3, 31.0, 29.0, 25.95, 25.94, 21.8, 21.74, 21.70, 21.5, 18.3, -5.5, -5.5; **HRMS (DART):** Calcd for $C_{29}H_{50}NO_5Si$ (MH^+): 520.3453; found: 520.3436.

Scheme S8. Derivatization of **3.21e-Minor** and Crystal Structure of **3.34e-Minor**





1-Benzyl-3-(1,4-diisopropoxy-1,4-dioxobutan-2-yl)-4-(hydroxymethyl)piperidin-1-ium chloride (3.34e-minor)

3.34e-Minor was synthesized by the following procedure. To a solution of **3.21e-minor** (150 mg, 0.3 mmol) in THF (10 mL) was added $Et_3N(HF)_3$ (0.3 mL), dropwise. The reaction was allowed to stir at 22 °C for 12 hours. The reaction mixture was concentrated and filtered through a plug of Celite using DCM as solvent. The unpurified product was then subjected to flash silica gel column chromatography (EtOAc:hexanes = 9:1) to afford diisopropyl 2-(1-benzyl-4-(hydroxymethyl)piperidin-3-yl)succinate **3.34e-minor-int** as a colorless oil (116 mg, 95%).

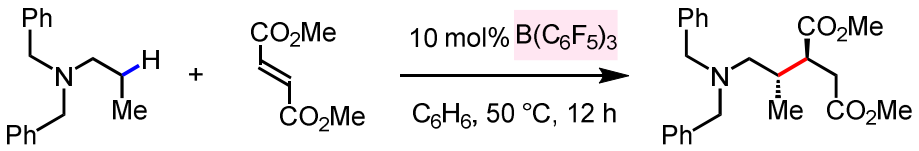
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, *J* = 4.5 Hz, 4H), 7.21 (q, *J* = 4.5 Hz, 1H), 4.98 (p, *J* = 6.3 Hz, 1H), 4.90 (p, *J* = 6.2 Hz, 1H), 3.73 (dd, *J* = 10.9, 4.4 Hz, 1H), 3.59 (dd, *J* = 10.9, 5.9 Hz, 1H), 3.50 (d, *J* = 13.1 Hz, 1H), 3.38 (d, *J* = 13.1 Hz, 1H), 3.17 (dt, *J* = 11.6, 3.7 Hz, 1H), 2.87 (d, *J* =

11.2 Hz, 1H), 2.68 – 2.48 (m, 2H), 2.32 (dd, *J* = 16.6, 3.3 Hz, 1H), 2.10 – 2.03 (m, 1H), 1.99 (t, *J* = 11.3 Hz, 1H), 1.79 (dt, *J* = 27.4, 12.1 Hz, 2H), 1.61 – 1.46 (m, 1H), 1.45 – 1.36 (m, 1H), 1.26 (t, *J* = 7.6 Hz, 1H), 1.21 (t, *J* = 6.3 Hz, 6H), 1.14 (d, *J* = 6.2 Hz, 3H), 1.04 (d, *J* = 6.2 Hz, 3H).

3.34e-Minor-int was then diluted in ethyl ether (0.10 mL) and 2.0 M HCl in ethyl ether was added dropwise to the solution until a white precipitate was formed. The solid was allowed to precipitate out of solution, whereupon the solvent was removed *in vacuo* to afford **3.34e-minor** as a white solid. **3.34e-Minor** was recrystallized using the vapor-vapor diffusion method, using *i*-PrOH to dissolve the product in an inner vial, and ethyl ether as the precipitant placed in the outer vial in order for slow diffusion to occur into the inner vial. The solution was cooled to 0 °C, whereupon a crystal was obtained for X-ray crystallography. The X-ray crystallographic analysis revealed that the relative configuration of **3.34e-minor** is (*R,R,S*) or (*S,S,R*). The relative configuration of products **3.21e-minor**, **3.21i-minor**, and **3.21t-minor** were assigned in analogy.

3.6.3.3. Determination of the Relative Configuration of 3.21b-Major

The relative configuration of **3.21b-major** was determined by the X-ray crystallographic analysis of **3.34b-major.**



3.19b, 0.2 mmol **3.20d**, 0.3 mmol **3.34b**, 43% yield 2.6:1 dr

To a 15 mL oven-dried pressure vessel was added dibenzylpropanamine **3.19b** (0.40 mmol), $B(C_6F_5)_3$ (10 mol%), dimethylfumarate **3.20d** (0.60 mmol) and benzene (0.40 mL) under a nitrogen atmosphere. The reaction mixture was placed in an oil bath at 50 °C and was allowed to stir for 12 hours. Upon completion, the solution was cooled to 22 °C and concentrated *in vacuo.* The ^{1}H NMR analysis of the unpurified product mixture revealed that **3.34b** was obtained as a mixture of diastereomers in 2.6:1 ratio. After purification by flash silica gel column chromatography (ethyl ether:hexanes = 1:19), **3.34b** was obtained as a mixture of diastereomers (66 mg, 43%). Further purification was carried out by PTLC using ethyl ether:DCM = 1:49 as the eluent to separate **3.34b-major** and **3.34b-minor**. The major diastereomer was isolated as a white solid (45 mg, 29% yield).

Dimethyl 2-(1-(dibenzylamino)propan-2-yl)succinate (3.34b-major)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 (d, *J* = 6.7 Hz, 4H), 7.29 (t, *J* = 7.5 Hz, 4H), 7.22 (t, *J* = 7.1 Hz, 2H), 3.78 (d, *J* = 13.2 Hz, 2H), 3.67 (s, 6H), 3.38 (d, *J* = 11.9 Hz, 1H), 3.26 (d, *J* = 13.3 Hz, 2H), 2.37 (dd, *J* = 16.8, 11.5 Hz, 2H), 2.24 (t, *J* = 11.5 Hz, 1H), 2.14 (dd, *J* = 13.0, 5.5 Hz, 1H), 1.51 (dd, *J* = 16.9, 2.9 Hz, 1H), 0.71 (d, *J* = 6.9 Hz, 3H).

The major diastereomer was then recrystallized using DCM:hexanes = 1:10 to afford a crystal for the X-ray analysis. The X-ray crystallographic analysis revealed that the relative configuration of **3.34b-major** is (*R,R*) or (*S,S*). The relative configuration of **3.21b-major** was assigned in analogy.

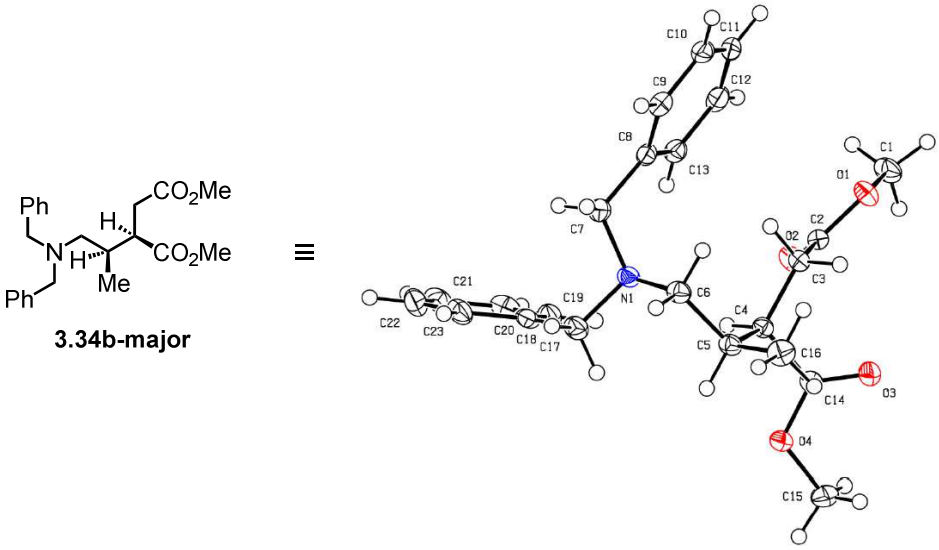


Figure S1. X-ray crystal structure of **3.34b-major**

3.6.3.4. Determination of the Relative Configuration of 3.22a

The relative configuration for **3.22a** was determined by NOESY experiments. The following are the NOE spectrum and assignments (Figure S2).

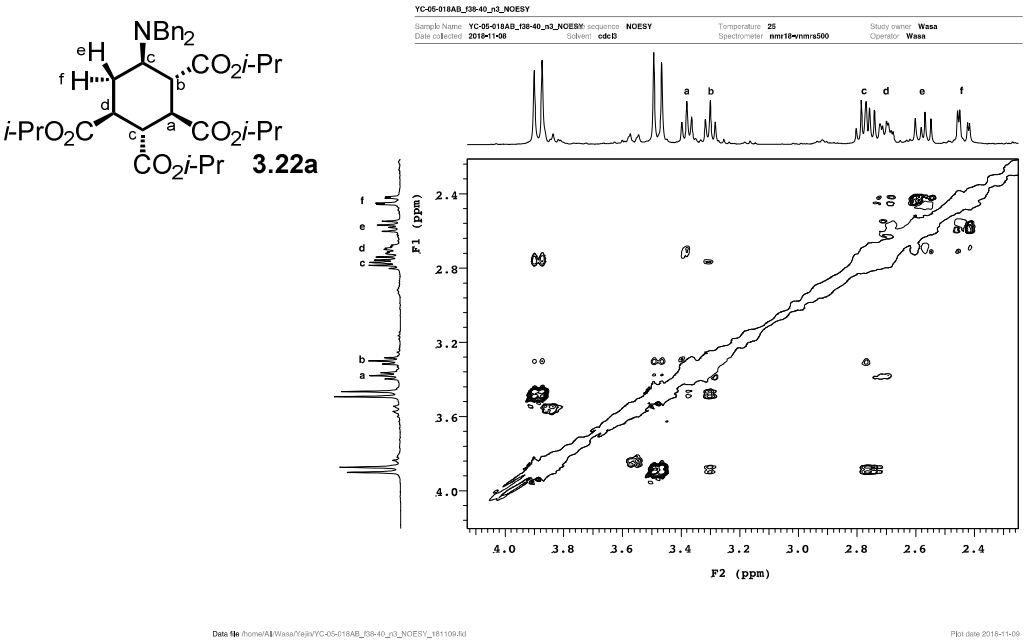


Figure S2. 2D NOESY spectra of **3.22a**

3.6.3.5. Determination of the Relative Configuration of 3.21p-Major

The relative configuration for **3.21p-major** was determined by NOESY experiments. The following are the NOE spectrum and assignments (Figure S3).

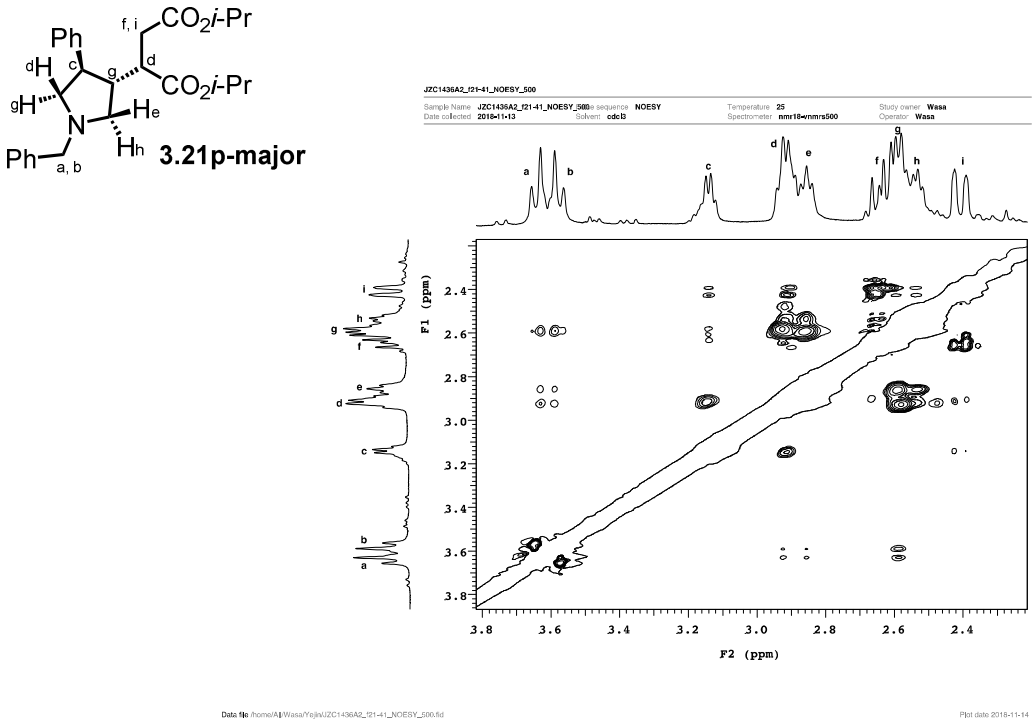


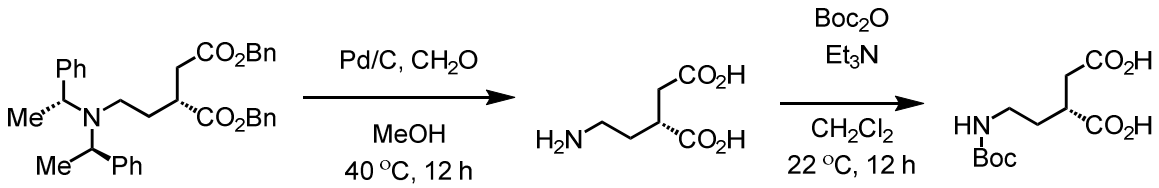
Figure S3. 2D NOESY spectra of **3.21p-major**

The relative configuration of the pyrrolidine substituents of **3.21p-major** was assigned to be *anti.*

3.6.4. Determination of Absolute Configuration

3.6.4.1 Determination of the Absolute Configuration of Product 3.21o-(*R,R,R*).

We carried out the following studies in order to determine the absolute configuration of product **3.21o**.



3.21o-major **3.34o-major-int** **3.34o-major**

The derivatization of the major diastereomer of **3.21o** was performed based on a method previously reported in the literature.[28] **3.21o-Major** (79 mg, 0.14 mmol) was dissolved in a solution of 4.4% formic acid in MeOH (3.0 mL), whereupon Pd/C (10%, 7.9 mg) was added. The reaction mixture was placed in an oil bath at 40 °C and was allowed to stir for 12 hours. After the solution was cooled down to 22 °C, the suspension was filtered through a pad of Celite using DCM as solvent and the mixture was concentrated to remove the solvent and volatile side products to obtain the product **3.34o-major-int** as a colorless oil (23 mg, >95% yield).

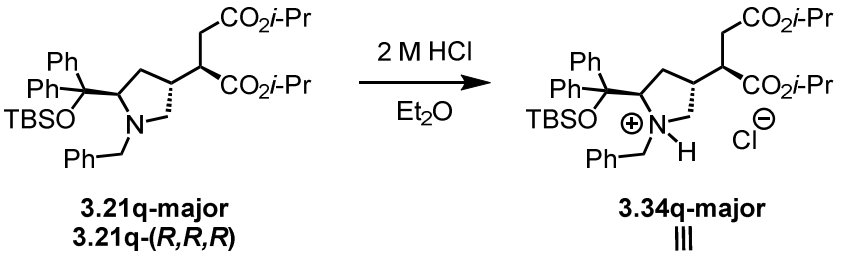
2-(2-Aminoethyl)succinic acid **3.34o-major-int** was then dissolved in DCM, whereupon Et_3N (20 µL, 0.15 mmol) and di-*tert*-butyl dicarbonate (30 µL, 0.15 mmol) were added, dropwise. The reaction mixture was allowed to stir at 22 °C for 12 hours. Upon completion, the unpurified mixture was concentrated to remove the solvent and volatile side products to obtain the product **3.34o-major** as a colorless oil (25 mg, 88% yield). $[\alpha]^{25}_{D}$ = + 27.6° (c = 1.0, acetone). Based on the observed optical rotation value, the absolute configuration of the major diastereomer was assigned in analogy as **3.21o-(*R,R,R*)**.[28]

[28] Davies, S. G.; Epstein, S. W.; Garner, A. C.; Ichihara, O.; Smith, A. D. *Tetrahedron: Asymmetry* **2002**, *13*, 1555–1565.

3.6.4.2. Determination of the Absolute Configuration of 3.21q-(*R*,*R*,*R*)

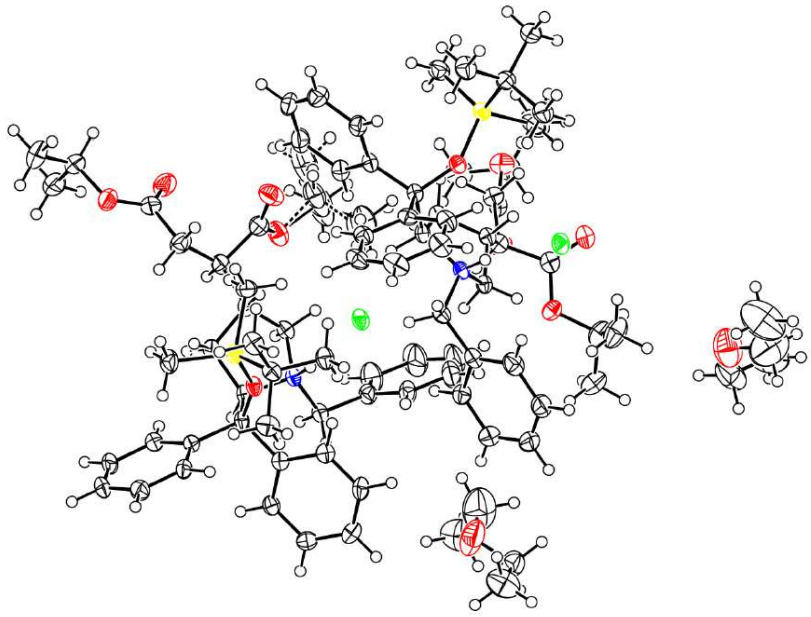
The absolute configuration of **3.21q-(*R*,*R*,*R*)** was determined by the X-ray crystallographic analysis of **3.34q-major** (Scheme S9).

Scheme S9. Derivatization of **3.21q-Major** and Crystal Structure of **3.34q-Major**



3.21q-major
3.21q-(*R*,*R*,*R*)

3.34q-major



(2*R*,4*R*)-1-Benzyl-2-(((*tert*-butyldimethylsilyl)oxy)diphenylmethyl)-4-((*R*)-1,4-diisopropoxy-1,4-dioxobutan-2-yl)pyrrolidin-1-ium chloride (3.34q-major)

11i-major was synthesized by the following procedure. **3.21q-(*R*,*R*,*R*)** was diluted in ethyl ether (0.2 mL) and 2.0 M HCl in ethyl ether was added dropwise to the solution until a white precipitate was formed. The solid was allowed to precipitate out of solution, whereupon the solvent was removed *in vacuo* to afford **3.34q-major** as a white solid. **3.34q-Major** was then recrystallized using DCM:ethyl ether = 1:10 and cooled to 0 °C to afford a crystal for X-ray analysis. The X-ray

crystallographic analysis revealed that the absolute configuration of **3.34q-major** is (*R,R,R*).

3.6.4.3. Determination of the Absolute Configuration of 3.21r-(*S,S,R,S*)

The absolute configuration of **3.21r-(*S,S,R,S*)** was determined through 2D NMR studies. The following are the spectra and assignments (Figures S4–6).

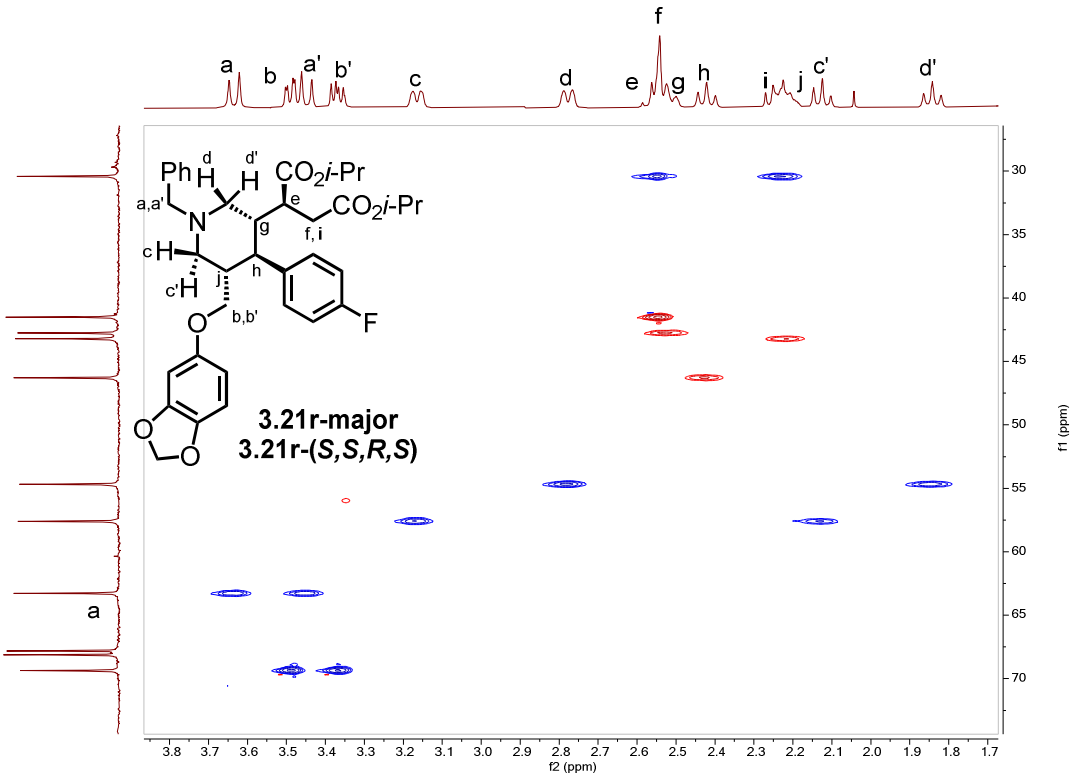


Figure S4. 2D HSQCAD spectra of **3.21r-major**

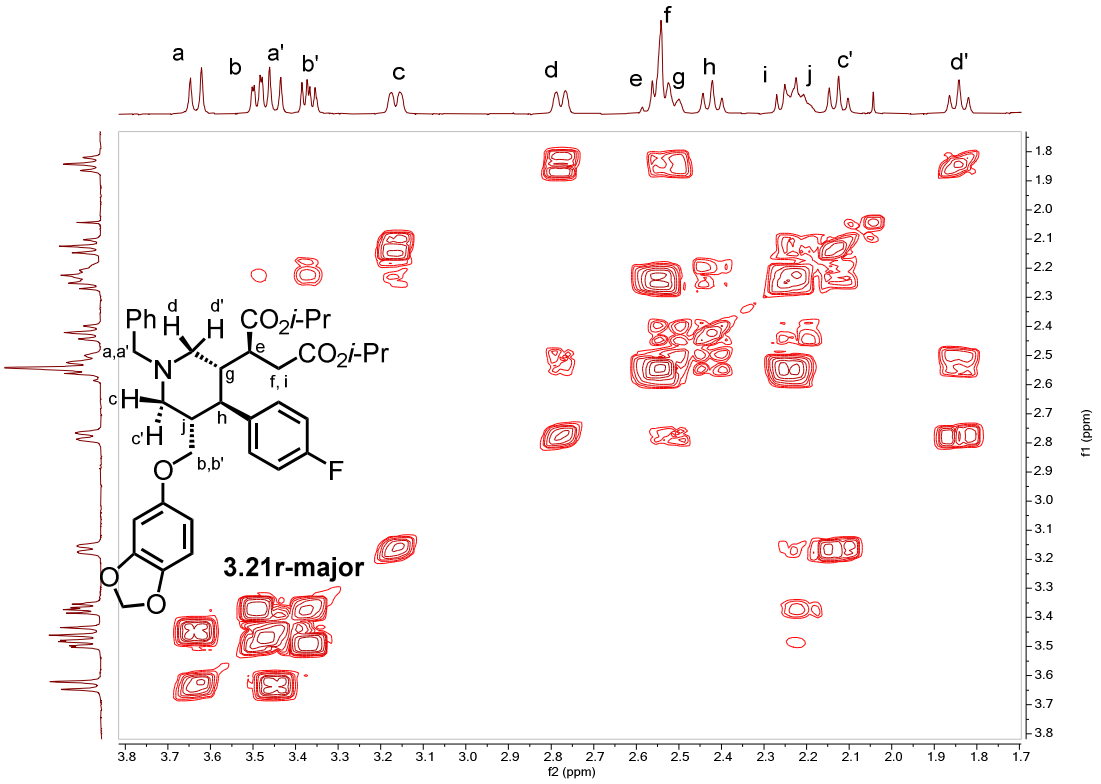


Figure S5. 2D COSY spectra of **3.21r-major**

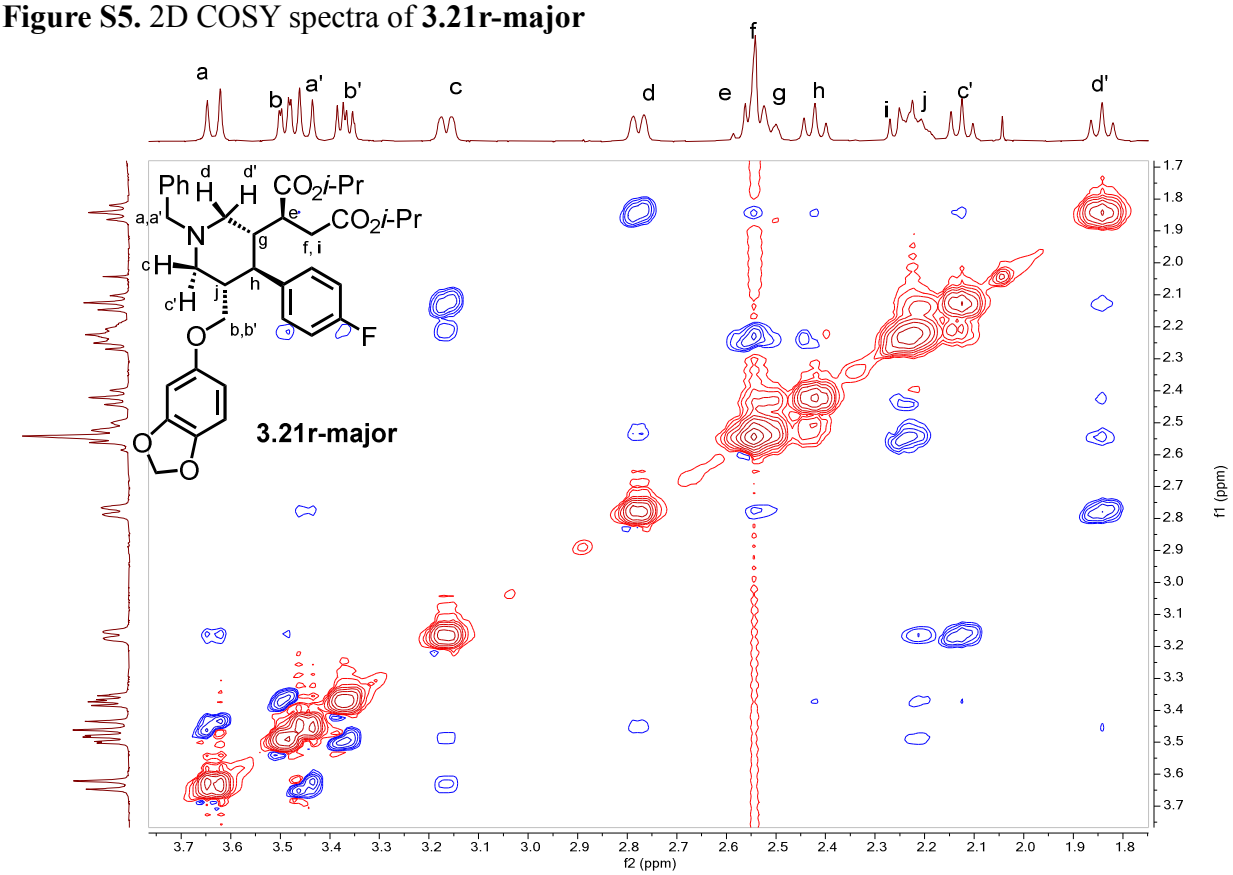
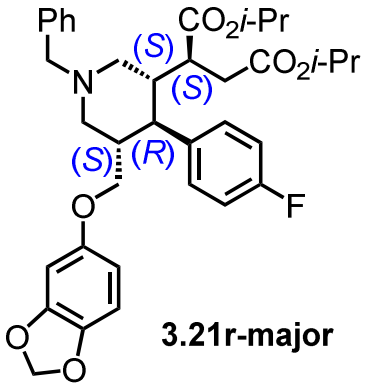


Figure S6. 2D NOESY spectra of **3.21r-major**

The absolute configuration of **3.21r-major** was assigned to be (*S,S,R,S*) by the 2D NMR analyses and in analogy to **3.21e-major** (See **Section 3.6.3.2**).

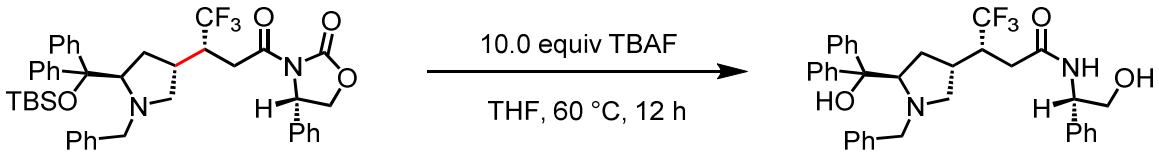


3.21r-major

3.6.4.4. Determination of the Absolute Configuration of 3.24b-(*R*,*R*,*R*,*S*)

The absolute configuration of **3.24b-(*R*,*R*,*R*,*S*)** was determined by the X-ray crystallographic analysis of **3.35b** (Scheme S10).

Scheme S10. Derivatization of **3.35b-(*R*,*R*,*R*,*S*)**.



3.24b **3.35b**

(*R*)-3-((3*R*,5*R*)-1-Benzyl-5-(hydroxydiphenylmethyl)pyrrolidin-3-yl)-4,4,4-trifluoro-*N*-((*S*)-2-hydroxy-1-phenylethyl)butanamide (3.35b)

11a was synthesized by the following procedure. To a solution of **3.24b** (371 mg, 0.50 mmol) in THF (5.0 mL) was added TBAF (2.0 M, 2.5 mL), dropwise. The reaction was placed in an oil bath at 60 °C and was allowed to stir for 12 hours. After the reaction mixture was cooled down to 22 °C, it was quenched with $NaHCO_3$ (aq.) and extracted with DCM (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The unpurified product was then subjected to flash silica gel column chromatography (EtOAc:hexanes = 1:4) to afford **3.35b** as a white solid (120 mg, 40%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 7.3 Hz, 2H), 7.51 (d, *J* = 7.0 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.29 – 7.23 (m, 5H), 7.23 – 7.07 (m, 7H), 6.97 (d, *J* = 6.2 Hz, 2H), 6.27 (d, *J* = 6.9 Hz, 1H), 4.90 (dt, *J* = 6.7, 4.8 Hz, 1H), 3.99 (dd, *J* = 10.3, 3.1 Hz, 1H), 3.77 (d, *J* = 4.9 Hz, 2H), 3.11 (d, *J* = 12.5 Hz, 1H), 3.06 (br, 1H), 2.95 (d, *J* = 12.6 Hz, 1H), 2.77 – 2.65 (m, 1H), 2.26 – 2.14 (m, 3H), 2.10 (dd, *J* = 15.9, 4.0 Hz, 1H), 1.90 (ddd, *J* = 12.5, 6.6, 3.0 Hz, 1H), 1.81 (qd, *J* = 10.2, 3.5 Hz, 1H); **^{19}F NMR (470 MHz, $CDCl_3$):** δ -69.28 (d, *J* = 8.7 Hz).

3.35b was recrystallized using the vapor-vapor diffusion method, using benzene to dissolve the product in an inner vial, and pentane as the precipitant placed in the outer vial in order for slow diffusion to occur into the inner vial. The solution was cooled to 0 °C, whereupon a crystal was obtained for X-ray crystallography (Figure S7). The X-ray crystallographic analysis revealed that the absolute configuration of **3.35b** is (*R,R,R,S*).

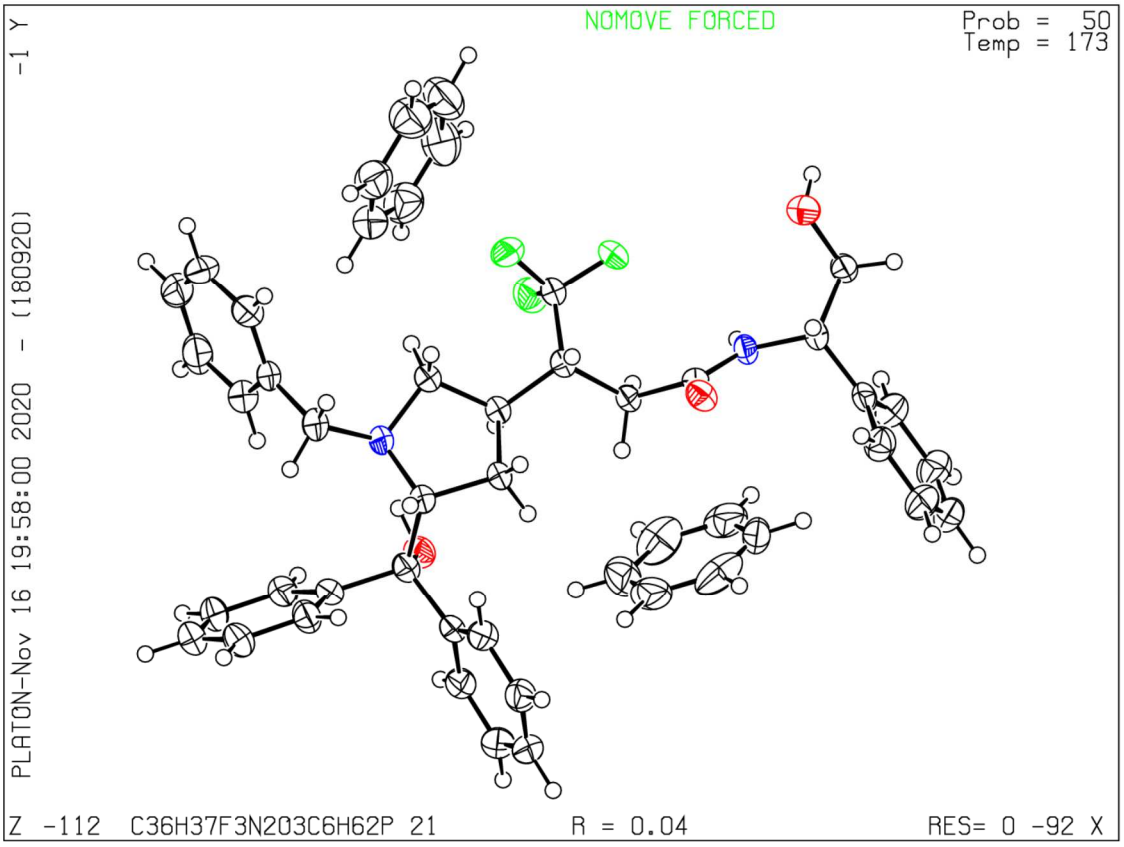
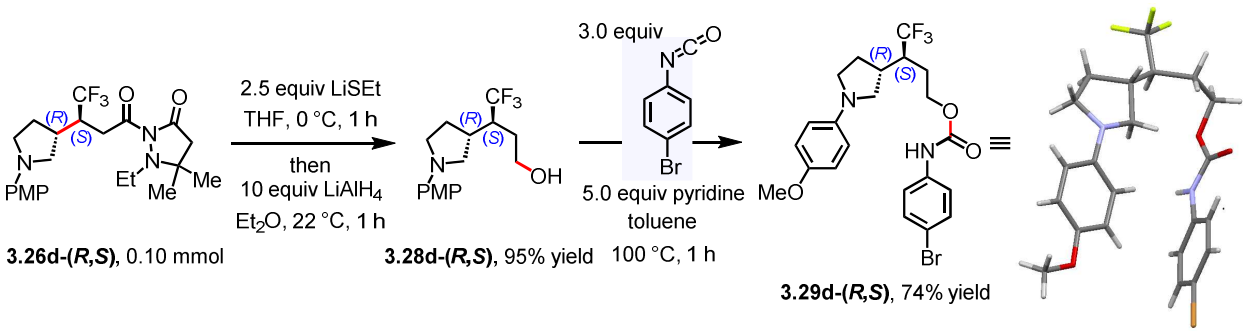


Figure S7. Crystal structure of **3.35b**

3.6.4.5. Determination of the Absolute Configuration of 3.26d-(*R*,*S*)

The absolute configuration of **3.26d-(*R*,*S*)** was determined by X-ray crystallographic analysis of **3.29d-(*R*,*S*)** (Scheme S11).[29]

Scheme S11. Derivatization of **3.26d-(*R*,*S*)** and Crystal Structure of **3.29d-(*R*,*S*)**



(*S*)-4,4,4-Trifluoro-3-((*R*)-1-(4-methoxyphenyl)pyrrolidin-3-yl)butan-1-ol (3.28d-(*R*,*S*))

A solution of EtSH (0.51 g, 8.2 mmol, 3.4 equiv) in THF (0.1 M) was cooled to –78 °C and treated with *n*-BuLi (3.8 mL, 6.0 mmol, 1.6 M in hexane, 2.5 equiv). The reaction was allowed to stir at 0 °C for 30 min. A solution of the **3.26d-(*R*,*S*)** (1.04 g, 2.4 mmol, 1.0 equiv) in THF (0.060 M) was then added dropwise. The reaction was allowed to stir at 0 °C until the consumption of the starting material was complete as monitored by TLC (0.5 – 1 h). The reaction was quenched with saturated NH_4Cl (aq.) and the phases separated. The aqueous layer was extracted with ethyl ether (x 3), the combined organic layers were dried over $MgSO_4$, and the solvent removed by rotary evaporation. The crude product was then dissolved in ethyl ether (0.10 M) and added to a suspension of $LiAlH_4$ (0.29 g, 7.2 mmol, 3.0 equiv) in ethyl ether at 22 °C. The mixture was stirred until the consumption of the starting material was monitored by TLC (0.5 – 2 h). The reaction was carefully quenched by the addition of water at 0 °C. The aqueous layer was then extracted with ethyl ether (x 3) and the combined organic layers were dried over $MgSO_4$ and the solvents removed

[29] Petrone, D. A.; Isomura, M.; Franzoni, I.; Rössler, S. L.; Carreira, E. M. *J. Am. Chem. Soc.* **2018**, *140*, 4697–4704.

to yield the crude product, which was purified by flash silica gel column chromatography.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.85 (d, *J* = 9.0 Hz, 2H), 6.53 (d, *J* = 9.0 Hz, 2H), 3.82 (dt, *J* = 12.0, 6.4 Hz, 1H), 3.79 – 3.71 (m, 4H), 3.42 (t, *J* = 8.4 Hz, 1H), 3.36 (td, *J* = 8.7, 1.8 Hz, 1H), 3.26 (td, *J* = 9.4, 6.6 Hz, 1H), 3.06 (t, *J* = 9.1 Hz, 1H), 2.67 – 2.55 (m, 1H), 2.41 (tdd, *J* = 9.7, 6.5, 2.8 Hz, 1H), 2.22 (dt, *J* = 13.0, 6.7 Hz, 1H), 1.96 – 1.75 (m, 3H), 1.43 (s, 1H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 151.3, 142.8, 128.4 (q, *J* = 281.0 Hz), 115.2, 112.7, 60.7, 56.1, 51.6, 48.2, 42.5 (q, *J* = 24.9 Hz), 38.0, 30.3, 29.7; **^{19}F NMR (470 MHz, $CDCl_3$):** δ -68.24 (d, *J* = 9.2 Hz); **IR (neat):** ν 3385, 2933, 2831, 1514, 1485, 1371, 1239, 1158, 1126, 1039, 812 cm^{-1}; **HRMS (DART):** Calcd for $C_{15}H_{21}F_3NO_2$ (MH^+): 304.1519; found: 304.1519; **Specific Rotation $[\alpha]^{25}_D$** = -4.5° (c = 1.0, DCM).

(*S*)-4,4,4-Trifluoro-3-((*R*)-1-(4-methoxyphenyl)pyrrolidin-3-yl)butyl(4 bromophenyl)carbamate (3.29d-(*R,S*))

To a solution of **3.28d-(*R,S*)** (330 mg, 1.1 mmol, 1.0 equiv.) in toluene (0.035 M) were added *p*-bromophenyl isocyanate (416 mg, 3.3 mmol, 3.0 equiv.) and pyridine (434 mg, 5.5 mmol, 5.0 equiv.). The resulting heterogeneous solution was placed in an oil bath at 100 °C and was allowed to stir for 1 hour. The solution was then cooled to 22 °C and filtered through a short plug of Celite using DCM. The filtrate was concentrated and the residue was purified by flash silica gel column chromatography (EtOAc:hexanes = 1:9) to afford compound **3.29d-(*R,S*)** (406 mg, 74%) as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41 (dd, *J* = 8.8, 1.4 Hz, 2H), 7.30 – 7.20 (m, 2H), 6.82 (d, *J* = 7.6 Hz, 2H), 6.62 (s, 1H), 6.50 (d, *J* = 7.6 Hz, 2H), 4.34 (dt, *J* = 11.8, 6.1 Hz, 1H), 4.27 – 4.16 (m, 1H), 3.75 (s, 3H), 3.42 (t, *J* = 8.4 Hz, 1H), 3.36 (t, *J* = 8.7 Hz, 1H), 3.25 (q, *J* = 8.8, 8.3 Hz, 1H),

3.05 (t, J = 8.9 Hz, 1H), 2.59 (h, J = 8.0 Hz, 1H), 2.40 – 2.28 (m, 1H), 2.22 (dt, J = 13.4, 6.8 Hz, 1H), 2.07 – 1.92 (m, 2H), 1.87 (p, J = 10.0 Hz, 1H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 153.1, 151.2, 142.6, 136.9, 132.1, 128.0 (q, J = 280.8 Hz), 120.4, 115.1, 112.6, 63.3, 56.0, 51.5, 48.0, 42.8 (q, J = 25.1 Hz), 37.9, 30.2, 26.5; **^{19}F NMR (564 MHz, $CDCl_3$):** δ -68.15 (d, J = 9.4 Hz); **IR (neat):** ν 3310, 2924, 2831, 1708, 1592, 1511, 1486, 1396, 1371, 1305, 1233, 1212, 1162, 1129, 1073, 1006, 890, 810, 764, 735, 700, 650, 626, 592, 521, 503, 458 cm^{-1}; **HRMS (DART):** Calcd for $C_{22}H_{25}BrF_3N_2O_3$ (MH^+): 501.0995; found: 501.0964; **Specific Rotation $[\alpha]^{25}_D$** = 20.0° (c = 1.0, DCM).

3.29d-(*R,S*) was recrystallized using the vapor-vapor diffusion method, using *i*-PrOH to dissolve the product in an inner vial, and pentane as the precipitant placed in the outer vial in order for slow diffusion to occur into the inner vial. The solution was cooled to 0 °C, whereupon a crystal was obtained for the X-ray crystallography (Scheme S11). The X-ray crystallographic analysis revealed that the absolute configuration of **3.29d** is (*R,S*).

3.6.4.6 Determination of the Absolute Configuration of 3.26e

The absolute configuration of **3.26e** was determined by analogy to **3.26d-major** and by 1D NOESY experiments. The following are the NOE spectra and assignments (**Figure S8**).

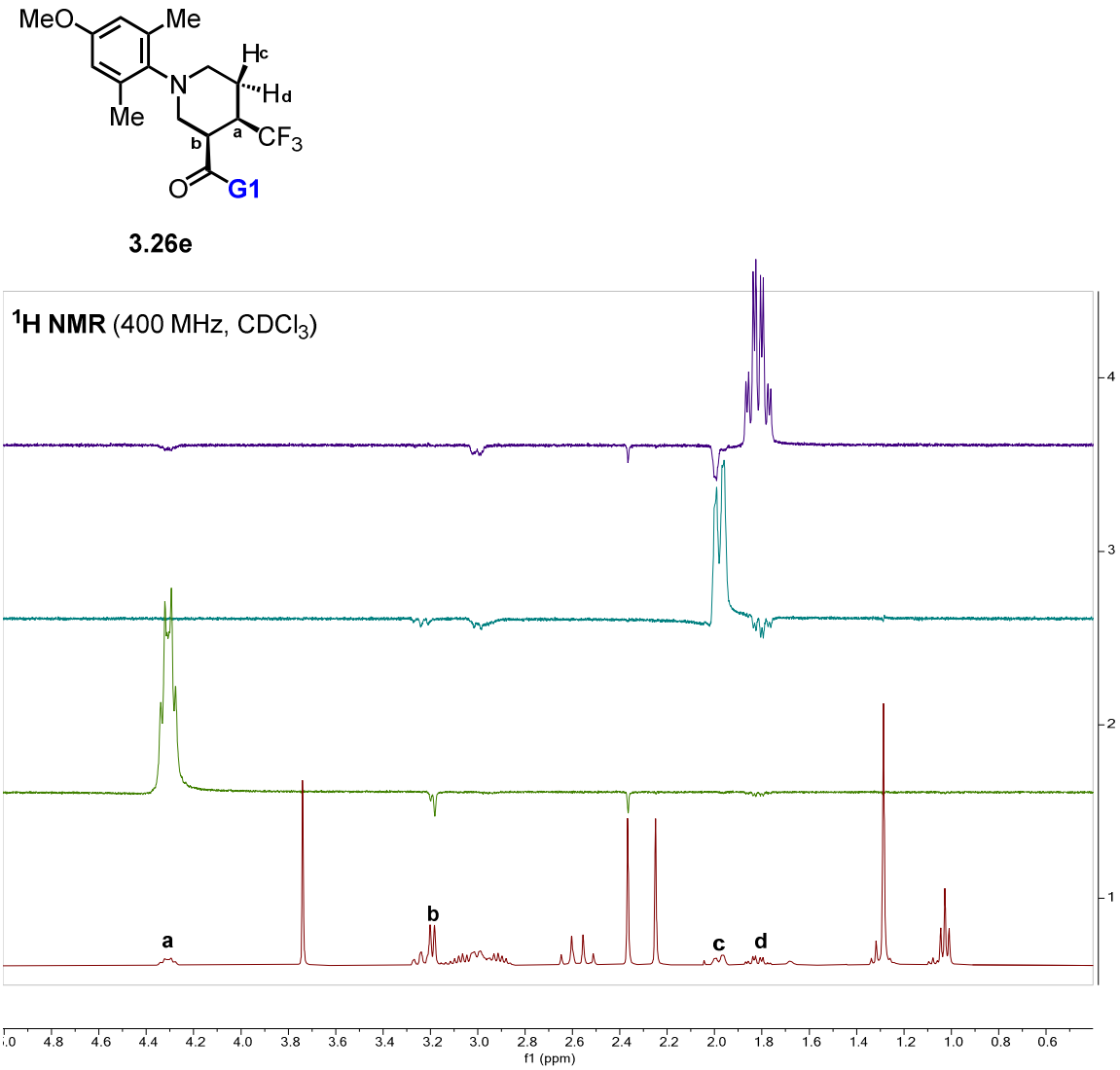
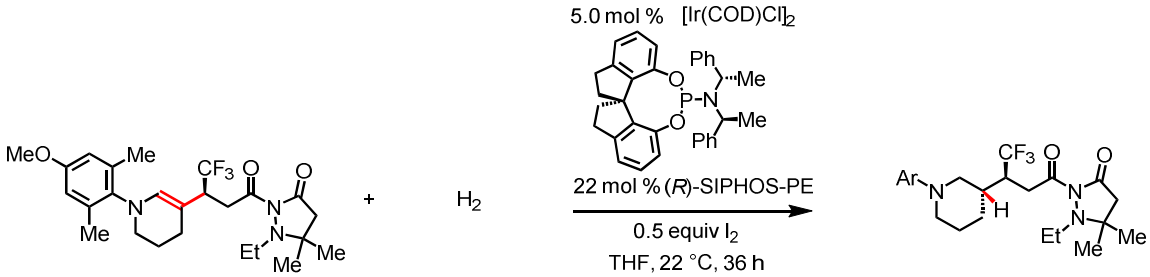


Figure S8. 1D NOESY spectra of **3.26e**

The NOE study revealed that the absolute configuration of **3.26e** is (*R,R*).

3.6.5. Derivatization of β-Alkylated Amines

3.6.5.1. Hydrogenation of 3.26f



3.26f, 0.10 mmol, 95:5 er 4.0 atm H_2 **3.30f**, 83% yield, 5.0:1 dr

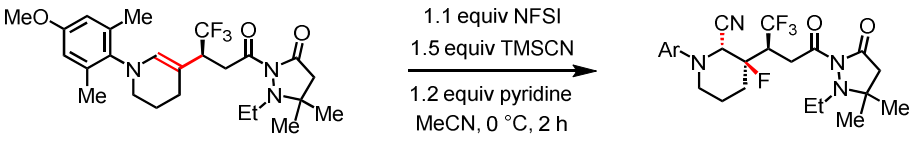
Diastereoselective hydrogenation of enamine **3.26f** was achieved following a previously reported literature.[19] In a nitrogen filled glove box, Ir[(COD)Cl]$_2$ (3.4 mg, 5.0 mol%), (*R*)-SIPHOS-PE (11.1 mg, 22 mol%), and 1.0 mL THF were added to an oven-dried 7.0 mL vial. The mixture was allowed to stir at 22 □ for 30 min and then transferred to an oven-dried 100 mL Schlenk flask. Then, I_2 (12.7 mg, 0.5 equiv), **3.26f** (48.2 mg, 0.10 mmol) and 1.0 mL THF were added to the mixture and then the Schlenk flask was taken out of the glove box. The nitrogen atmosphere in the Schlenk flask was replaced by hydrogen three times and finally hydrogen gas was charged at −200 □. The reaction mixture was slowly warmed up to 22 □ and was allowed to stir for 36 hours (under 4.0 atm H_2 pressure). ^{19}F NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was 5.0:1. After purification by flash silica gel column chromatography (EtOAc:hexanes = 1:3), **3.30f** was obtained as a mixture of diastereomers (40.0 mg, 83% yield). Further purification was carried out by PTLC using ethyl ether:hexanes = 2:1 as the eluent to obtain **3.30f-major**.

3.30f-Major. **^{1}H NMR (400 MHz, CDCl$_3$):** δ 6.58 (d, *J* = 3.0 Hz, 1H), 6.45 (d, *J* = 3.0 Hz, 1H), 3.74 (s, 3H), 3.23 (dd, *J* = 17.7, 6.2 Hz, 1H), 3.09 – 2.90 (m, 7H), 2.85 (d, *J* = 11.3 Hz, 1H), 2.63 – 2.53 (m, 2H), 2.26 (d, *J* = 13.2 Hz, 6H), 2.10 – 2.01 (m, 1H), 1.93 (d, *J* = 13.3 Hz, 1H), 1.75 –

1.61 (m, 2H), 1.31 – 1.26 (m, 7H), 1.04 (t, J = 7.1 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 175.49, 168.72, 156.49, 142.54, 138.95, 137.91, 128.12 (q, J = 281.1 Hz), 114.22, 113.39, 60.72, 55.37, 54.13, 50.83, 47.16, 44.07, 41.71 (q, J = 25.1 Hz), 37.44, 32.81, 28.72, 27.05, 25.94, 25.81, 20.21, 19.66, 12.83; **^{19}F NMR (376 MHz, $CDCl_3$):** δ -66.80 (d, J = 10.1 Hz); **IR (neat):** ν 2930, 2851, 1745, 1711, 1602, 1485, 1466, 1372, 1309, 1254, 1222, 1189, 1154, 1119, 1067, 990, 855, 616 cm^{-1}; **HRMS (DART):** Calcd for $C_{25}H_{37}F_3N_3O_3$ (MH^+): 484.2782; found: 484.2785; **Specific Rotation $[\alpha]^{25}_D$** = -8.0° (c = 0.35, DCM).

3.30f (major:minor = 1:1.3). **^{1}H NMR (400 MHz, $CDCl_3$, *peaks from diastereomers are merged*):** 6.58 (d, J = 3.1 Hz, 1H), 6.45 (d, J = 3.0 Hz, 1H), 3.74 (s, 3H), 3.28 – 3.15 (m, 1H), 3.10 – 2.92 (m, 7H), 2.89 – 2.80 (m, 1H), 2.67 – 2.51 (m, 2H), 2.29 – 2.21 (m, 6H), 2.11 – 1.99 (m, 1H), 1.97 – 1.84 (m, 1H), 1.76 – 1.60 (m, 2H), 1.33 – 1.25 (m, 7H), 1.12 – 1.01 (m, 3H); **^{19}F NMR (376 MHz, $CDCl_3$):** δ -66.80 (d, J = 10.1 Hz, *major*), -67.20 (d, J = 10.2 Hz, *minor*).

3.6.5.1. Fluorocyanation of 3.26f



3.26f, 0.1 mmol, 95:5 er

3.31f, 88% yield, 4.0:1 dr

Fluorocyanation of enamine **3.26f** was achieved following a previously reported literature.[20] To an oven-dried 10 mL round bottom flask was added NFSI (34.7 mg, 1.1 equiv), TMSCN (0.02 mL, 1.5 equiv) and 0.50 mL of MeCN. After the mixture was cooled to 0 □, pyridine (0.01 mL, 1.2 equiv) and **3.26f** (48.2 mg, 0.10 mmol) were added. The reaction mixture was allowed to stir at 0 □ for 1 hour. Upon completion, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl ether three times. The combined organic layer was washed with brine, dried with $MgSO_4$ and was concentrated *in vacuo*. The ^{19}F NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was 4.0:1. After purification by flash silica gel column chromatography (EtOAc:hexanes = 1:3), **3.31f** was obtained as a mixture of diastereomers (46.5 mg, 88% yield). Further purification was carried out by PTLC using EtOAc:hexanes = 1:3 as the eluent to separate **3.31f-major** and **3.31f-minor**.

3.31f-Major. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.56 (d, *J* = 3.1 Hz, 1H), 6.50 (d, *J* = 3.1 Hz, 1H), 4.15 (d, *J* = 4.9 Hz, 1H), 3.82 – 3.70 (m, 4H), 3.64 (t, *J* = 11.6 Hz, 1H), 3.47 (ddd, *J* = 19.1, 6.4, 2.3 Hz, 1H), 3.16 (dd, *J* = 19.4, 4.3 Hz, 1H), 3.06 – 2.92 (m, 3H), 2.62 (d, *J* = 17.3 Hz, 1H), 2.55 (d, *J* = 17.3 Hz, 1H), 2.47 (s, 3H), 2.35 – 2.24 (m, 4H), 2.19 – 2.01 (m, 2H), 1.77 – 1.67 (m, 1H), 1.33 – 1.24 (m, 7H), 1.04 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 175.5, 167.7, 157.4, 139.1, 138.95, 138.86, 126.4 (q, *J* = 281.9 Hz), 117.1 (d, *J* = 10.2 Hz), 114.7, 114.3, 92.3 (d, *J* = 193.6 Hz), 60.9, 58.8 (d, *J* = 29.9 Hz), 55.4, 47.5, 47.2, 44.6 (qd, *J* = 26.1, 21.4 Hz), 43.8, 31.8 (dd, *J* = 9.1, 2.6 Hz), 28.9 (dd, *J* = 22.4, 2.7 Hz), 26.1, 25.6, 21.6, 21.1, 19.5 (d, *J* = 7.0 Hz), 12.8;

^{19}F NMR (564 MHz, $CDCl_3$): δ -63.97 – -64.00 (m), -161.94; **IR (neat):** ν 2961, 2839, 1746, 1711, 1601, 1485, 1466, 1442, 1375, 1304, 1263, 1234, 1216, 1155, 1132, 1094, 1069,992, 975, 950, 930, 898, 856, 736, 619 cm^{-1}; **HRMS (DART):** Calcd for $C_{26}H_{35}F_4N_4O_3$ (MH^+): 527.2640; found: 527.2640; **Specific Rotation $[\alpha]^{25}_D$** = +6.9° (c = 1.0, DCM).

3.31f-Minor. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.58 (d, *J* = 3.0 Hz, 1H), 6.49 (d, *J* = 3.0 Hz, 1H), 4.50 (d, *J* = 20.3 Hz, 1H), 4.10 (tt, *J* = 9.8, 5.7 Hz, 1H), 3.74 (s, 3H), 3.45 (dd, *J* = 17.8, 5.1 Hz, 1H), 3.27 (ddd, *J* = 18.0, 6.5, 2.4 Hz, 1H), 3.19 – 3.03 (m, 2H), 3.01 (q, *J* = 7.1 Hz, 2H), 2.60 (d, *J* = 3.4 Hz, 2H), 2.40 – 2.26 (m, 7H), 2.09 – 1.95 (m, 1H), 1.89 – 1.63 (m, 3H), 1.31 (d, *J* = 1.7 Hz, 6H), 1.06 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 175.77, 166.98, 157.91, 140.77, 138.35, 138.06, 125.91 (q, *J* = 280.2 Hz), 114.72 (d, *J* = 1.9 Hz), 114.48, 113.98, 91.82 (d, *J* = 192.2 Hz), 60.72, 59.36 (dd, *J* = 20.1, 2.5 Hz), 55.28, 49.75, 47.10, 44.89 (p, *J* = 26.2 Hz), 44.16, 31.18 (dd, *J* = 6.7, 2.7 Hz), 29.12, 28.95, 25.87 (d, *J* = 13.1 Hz), 21.03 (d, *J* = 2.8 Hz), 19.65, 19.55, 12.73; **^{19}F NMR (470 MHz, $CDCl_3$):** δ -64.16 – -64.69 (m), -159.84; **IR (neat):** ν 2925, 2851, 1744, 1712, 1602, 1484, 1465, 1443, 1374, 1302, 1263, 1225, 1196, 1183, 1144, 1113, 1070, 1023, 992, 949, 855, 835, 796, 769, 734, 619, 458 cm^{-1}; **HRMS (DART):** Calcd for $C_{26}H_{35}F_4N_4O_3$ (MH^+): 527.2640; found: 527.2641; **Specific Rotation $[\alpha]^{25}_D$** = -8.3° (c = 0.50, DCM).

3.6.6. Mechanistic Studies for β-Amino C–H Alkylation Reaction

We have demonstrated that cooperative functions of $B(C_6F_5)_3$ and a chiral Lewis acid co-catalyst can promote highly enantioselective union of *N*-alkylamines and α,β-unsaturated compounds. To shed light on the mechanism of this enantioselective process, we embarked on investigations that were aimed at determining its turnover-limiting step, understanding the nature of hydride and proton transfer processes, and elucidating the origin of chemoselectivity between enamine and *N*-alkylamine products.

Following are the mechanistic studies that were carried out to obtain the necessary data:

Section 3.6.6.1.1: Determination of the reaction orders involving **3.25e**

Section 3.6.6.1.2: Detection of the catalyst resting state involving **3.25e**

Section 3.6.6.1.3: Kinetic isotope effect studies involving **3.25e**

Section 3.6.6.1.4: Hammett studies

Section 3.6.6.3: Monitoring the ratios at which different products are formed by the ^{1}H NMR studies.

Section 3.6.6.4.1: Determination of the reaction orders involving **3.25a**

Section 3.6.6.4.2: Detection of the catalyst resting state involving **3.25a**

Section 3.6.6.4.3: Kinetic isotope effect studies involving **3.25a**

3.6.6.1 Mechanistic Studies Involving 3.25e

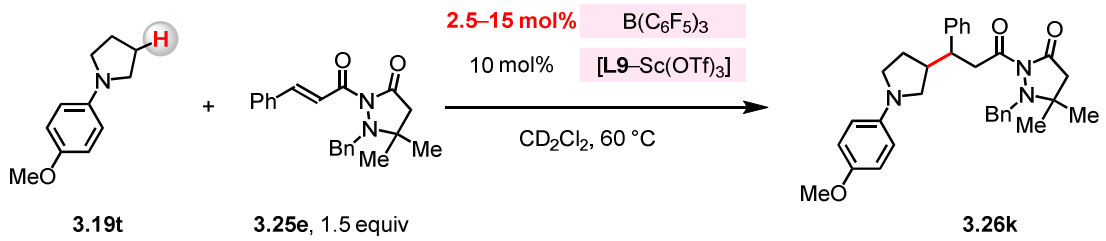
3.6.6.1.1 Determination of the Reaction Orders

For the β-C–H alkylation reaction involving 1-(4-methoxyphenyl)pyrrolidine **3.19t** and 1-benzyl-2-cinnamoyl-5,5-dimethylpyrazolidin-3-one **3.25e**, the reaction order of each reactant was studied through time course reaction monitoring by the ^{1}H NMR spectroscopic analysis.

3.6.6.1.1.1. Reaction Order of $B(C_6F_5)_3$

The reaction between **3.19t** and **3.25e** was performed using different concentrations of $B(C_6F_5)_3$ and the progress of each reaction was monitored by the ^{1}H NMR spectroscopy (Scheme S12).

Scheme S12. Determination of the Reaction Order of $B(C_6F_5)_3$



In a nitrogen-filled glove box, **L9**–$Sc(OTf)_3$ (51.4 mg, 10 mol%), **3.19t** (115.1 mg, 0.65 mmol), **3.25e** (326.1 mg, 1.5 equiv) and mesitylene (78.0 mg, 1.0 equiv) were weighed in an oven-dried 7.0 mL vial and the resulting mixture was dissolved in 3.25 mL of CD_2Cl_2 (**Stock Solution A**). In another oven-dried 7.0 mL vial, $B(C_6F_5)_3$ (30.7 mg, 0.060 mmol) was weighed and dissolved in 1.20 mL of CD_2Cl_2 (**Stock Solution B**). To each J-Young tube was added **Stock Solution A** (0.50 mL), **Stock Solution B** (0.05, 0.10, 0.15, 0.20, 0.25, or 0.30 mL) and CD_2Cl_2 (0.25, 0.20, 0.15, 0.10, 0.05 or 0 mL) to prepare the reaction samples containing different concentrations of $B(C_6F_5)_3$. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and the ^{1}H NMR spectra were acquired in the NMR spectrometer preheated at 60 °C using a pre-acquisition delay in array mode with a spectrum taken every 22 seconds for the length of the experiment. The data were processed using MestReNova software and peak integrations were

normalized using mesitylene as the internal standard.

Initial-rate kinetic analysis, which was determined based on the data points acquired in the first 600 seconds, showed that there is *second-order dependency* on $B(C_6F_5)_3$ concentration in the reaction between **3.19t** and **3.25e** (Figures S9, 10).

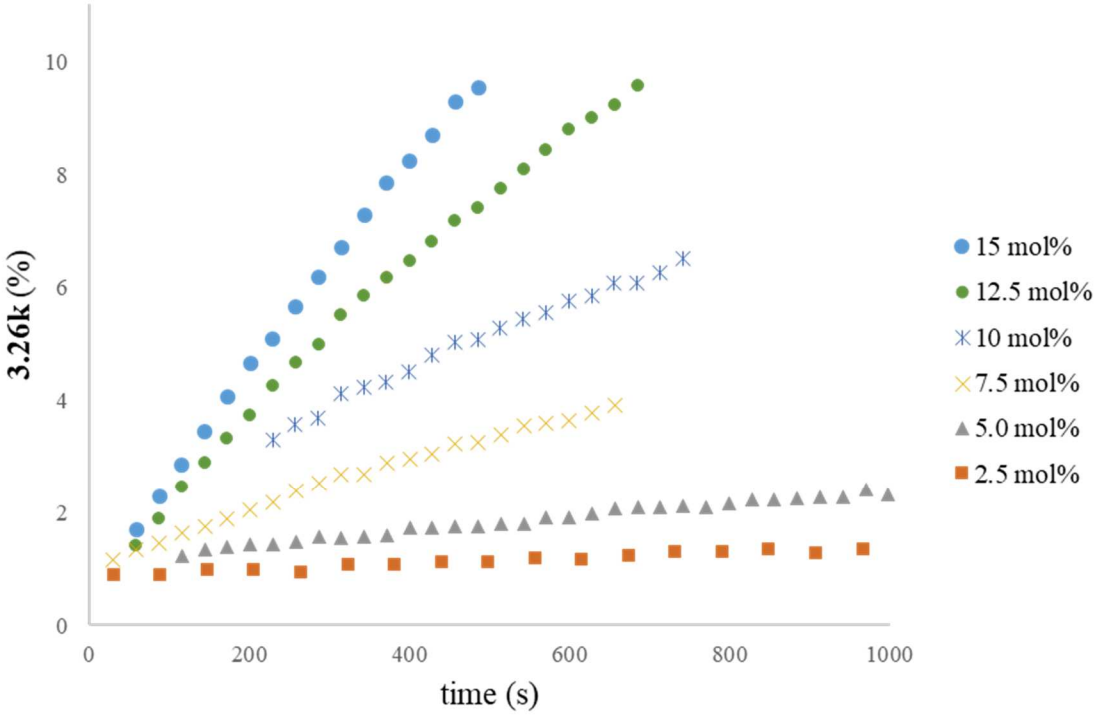


Figure S9. Monitoring the formation of **3.26k** under different concentrations of $B(C_6F_5)_3$

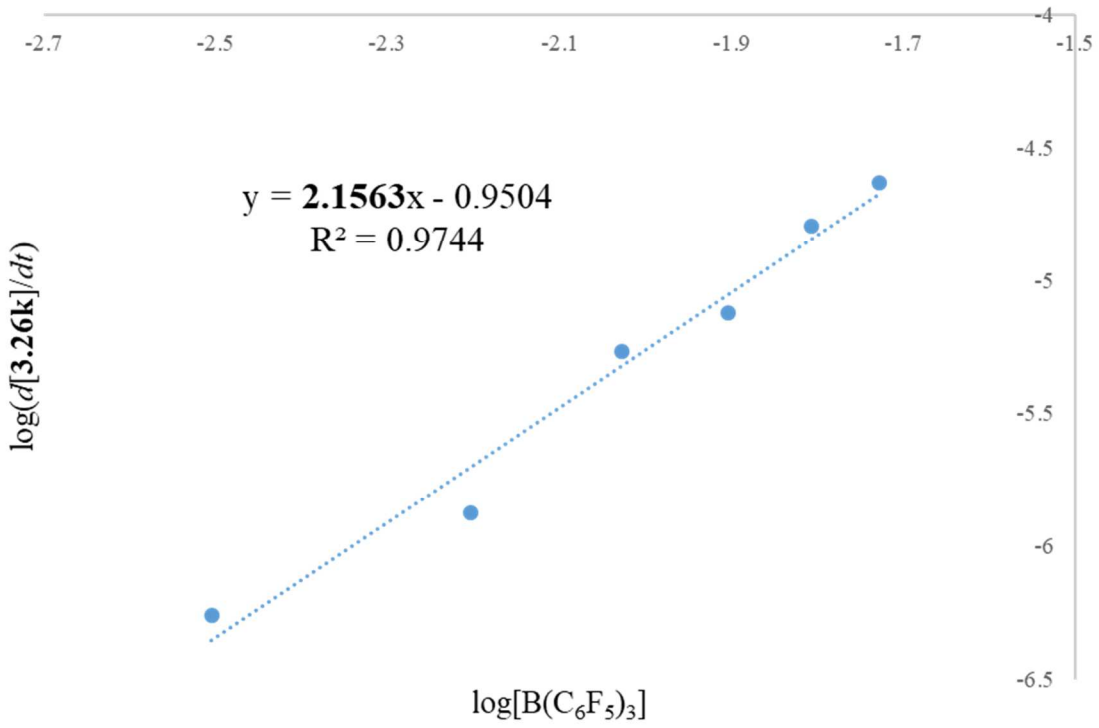
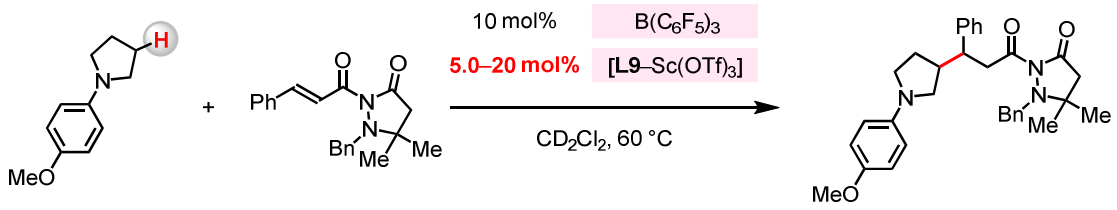


Figure S10. Log(rate) *vs* log[$B(C_6F_5)_3$] is employed to determine the initial reaction order for $B(C_6F_5)_3$. The result suggests that there is *second-order dependency* on $B(C_6F_5)_3$ concentration.

3.6.6.1.1.2. Reaction Order of L9–Sc(OTf)$_3$

The reaction between **3.19t** and **3.25e** was performed using different concentrations of **L9**–Sc(OTf)$_3$ and the progress of each reaction was monitored by the ^{1}H NMR spectroscopy (Scheme S13).

Scheme S13. Determination of the Reaction Order of **L9**–Sc(OTf)$_3$



In a nitrogen-filled glove box, B(C_6F_5)$_3$ (26.6 mg, 10 mol%), **3.19t** (92.0 mg, 0.52 mmol), **3.25e** (260.8 mg, 1.5 equiv) and mesitylene (26.6 mg, 1.0 equiv) were weighed in an oven-dried 7.0 mL vial and the resulting mixture was dissolved in 2.10 mL of CD_2Cl_2 (**Stock Solution A**). In another oven-dried 7.0 mL vial, **L9**–Sc(OTf)$_3$ (47.4 mg, 0.060 mmol) was weighed and dissolved in 1.20 mL of CD_2Cl_2 (**Stock Solution B**). To each J-Young tube was added **Stock Solution A** (0.40 mL), **Stock Solution B** (0.10, 0.20, 0.30 or 0.40 mL) and neat CD_2Cl_2 (0.30, 0.20, 0.10 or 0 mL) to prepare the reaction samples containing different concentrations of **L9**–Sc(OTf)$_3$. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and ^{1}H NMR spectra were acquired in the NMR spectrometer preheated at 60 °C using a pre-acquisition delay in array mode with a spectrum taken every 22 seconds for the length of the experiment. The data were processed using MestReNova software and peak integrations were normalized using mesitylene as the internal standard.

Initial-rate kinetic analysis, which was determined based on the data points acquired in the first 1200 seconds, showed that there is *zero-order dependency* on **L9**–Sc(OTf)$_3$ concentration in the reaction between **3.19t** and **3.25e** (Figures S11, 12).

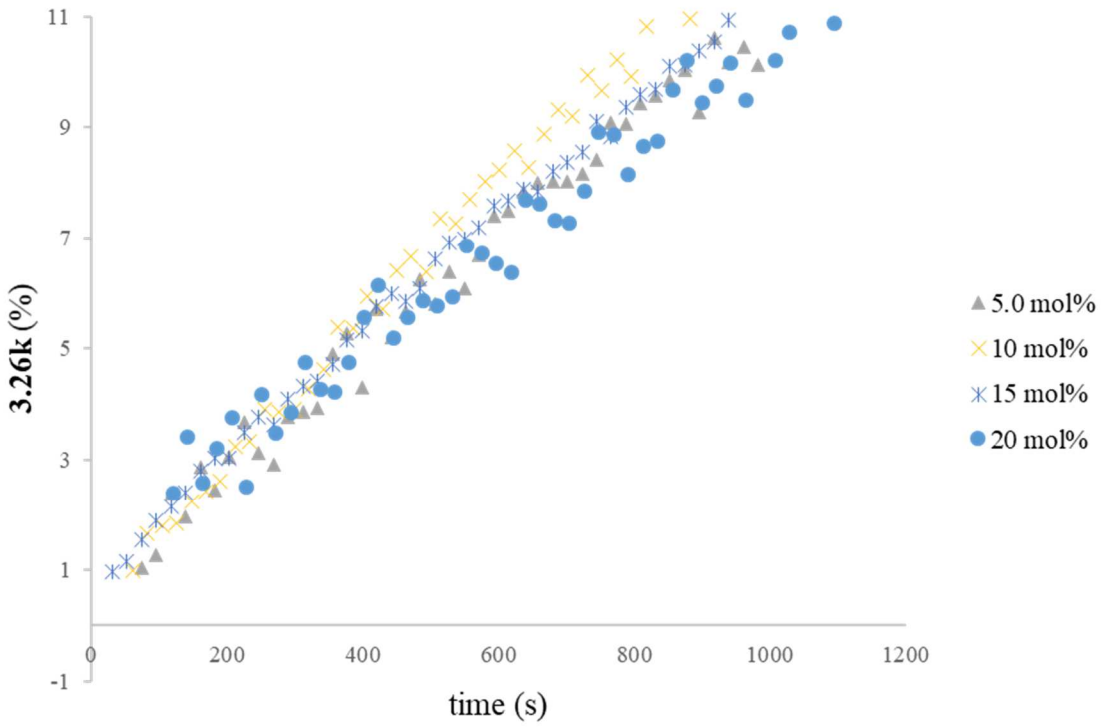


Figure S11. Monitoring the formation of **3.26k** under different concentrations of **L9**–$Sc(OTf)_3$

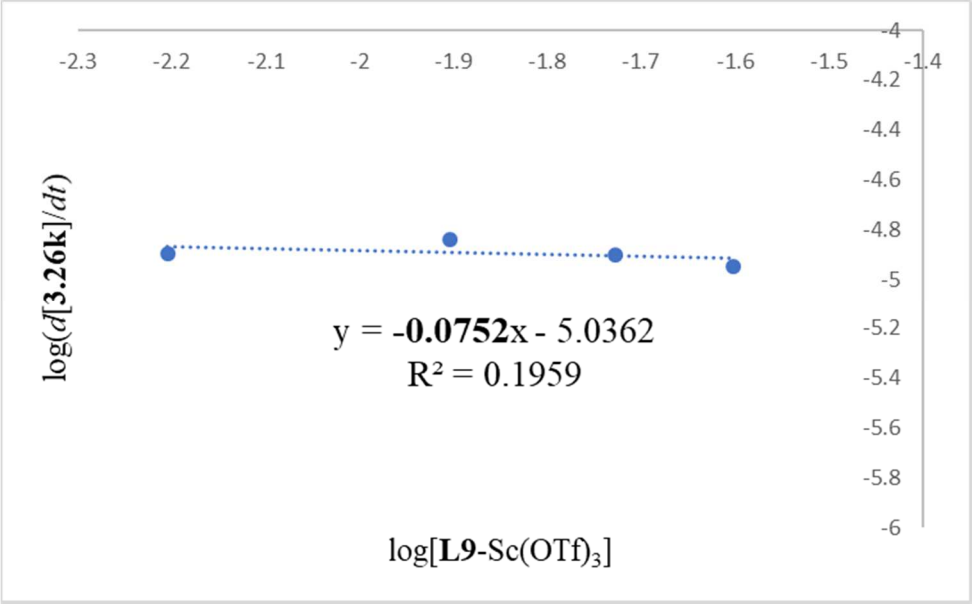
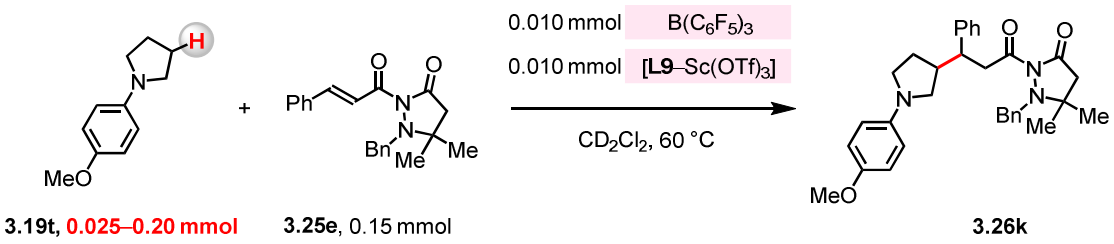


Figure S12. Log(rate) *vs* log[**L9**–Sc(OTf)$_3$] is employed to determine the initial reaction order for **L9**–Sc(OTf)$_3$. The result suggests that there is *zero-order dependency* on **L9**–Sc(OTf)$_3$ concentration.

3.6.6.1.1.3. Reaction Order of Amine

The reaction between **3.19t** and **3.25e** was performed using different concentrations of **3.19t** and the progress of each reaction was monitored by the ^{1}H NMR spectroscopy (Scheme S14).

Scheme S14. Determination of the Reaction Order of **3.19t**



In a nitrogen-filled glove box, $B(C_6F_5)_3$ (28.2 mg, 0.055 mmol), **L9**–$Sc(OTf)_3$ (43.5 mg, 0.055 mmol), **3.25e** (275.9 mg, 0.83 mmol) and mesitylene (66.1 mg, 0.55 mmol) were weighed in an oven-dried 7.0 mL vial and the resulting mixture was dissolved in 4.40 mL of CD_2Cl_2 (**Stock Solution A**). In 5 oven-dried 7.0 mL vials were added **3.19t** (4.4 mg, 8.9 mg, 17.7 mg, 26.6 mg or 35.4 mg). To each oven-dried vial containing **3.19t** was added **Stock Solution A** (0.80 mL) to prepare the reaction samples containing different concentrations of **3.19t**. The reaction mixture was then transferred to a J-Young tube. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and ^{1}H NMR spectra were acquired in the NMR spectrometer preheated at 60 °C using a pre-acquisition delay in array mode with a spectrum taken every 22 seconds for the length of the experiment. The data were processed using MestReNova software and peak integrations were normalized using mesitylene as the internal standard.

Initial-rate kinetic analysis, which was determined based on the data points acquired in the first 600 seconds, showed that there is *first-order dependency* on amine **3.19t** concentration in the reaction between **3.19t** and **3.25e** (Figures S13, 14).

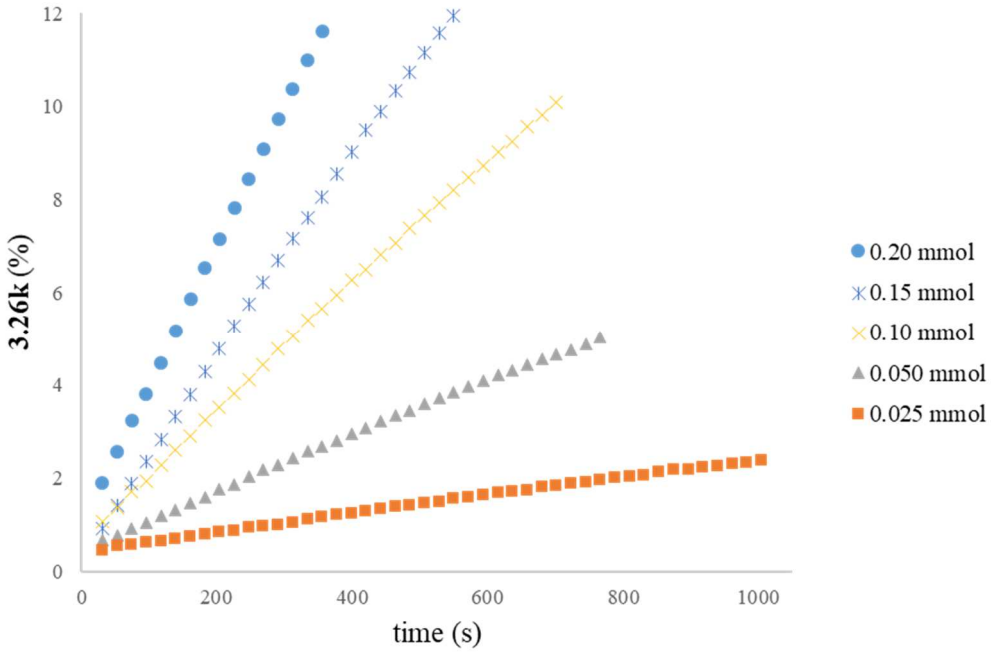


Figure S13. Monitoring the formation of **3.26k** under different concentrations of amine **3.19t**

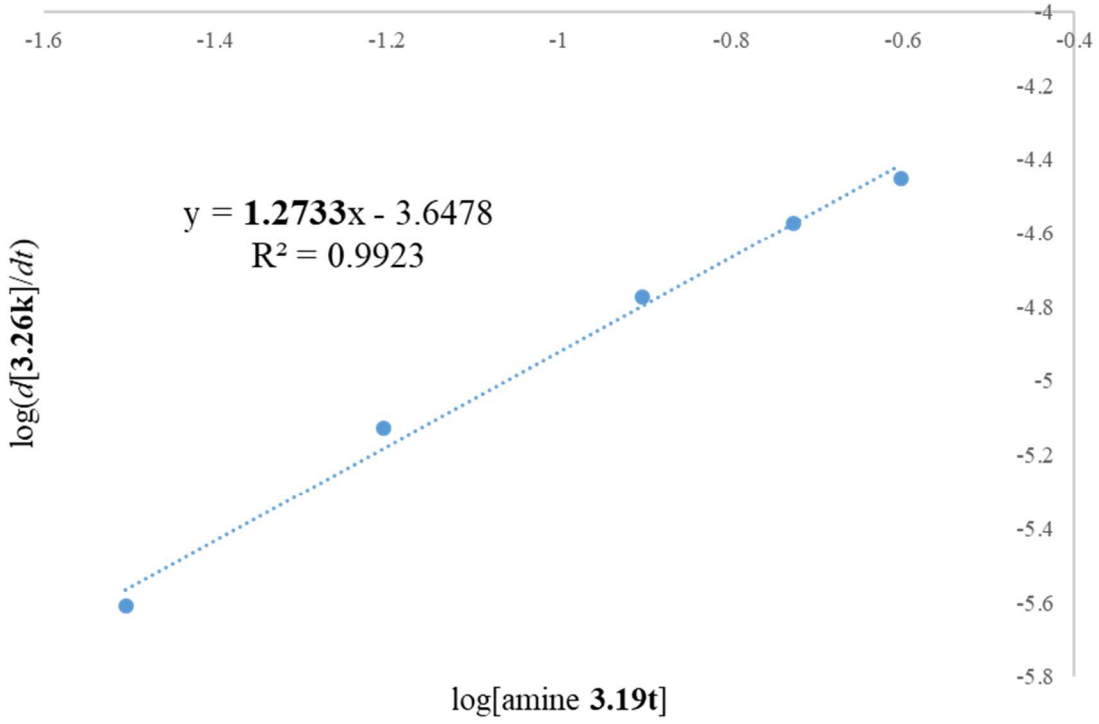
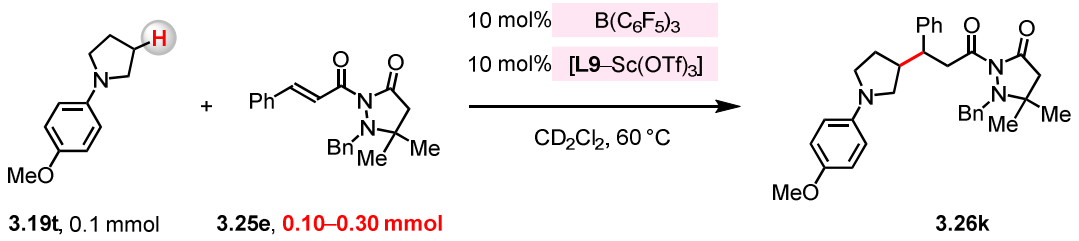


Figure S14. Log(rate) *vs* log[amine **3.19t**] is employed to determine the initial reaction order for amine **3.19t.** The result suggests that there is *first-order dependency* on **3.19t** concentration.

3.6.6.1.1.4. Reaction Order of α,β-Unsaturated Compound

The reaction between **3.19t** and **3.25e** was performed using different concentrations of **3.25e** and the progress of each reaction was monitored by the ^{1}H NMR spectroscopy (Scheme S15).

Scheme S15. Determination of the Reaction Order of **3.25e**



In a nitrogen-filled glove box, **L9**–$Sc(OTf)_3$ (49.0 mg, 10 mol%), **3.19t** (109.7 mg, 0.62 mmol), and mesitylene (74.4 mg, 1.0 equiv) were weighed in an oven-dried 7.0 mL vial and the resulting mixture was dissolved in 3.10 mL of CD_2Cl_2 (**Stock Solution A**). In another oven-dried 7.0 mL vial, $B(C_6F_5)_3$ (35.8mg, 0.70 mmol) was weighed and dissolved in 2.10 mL of CD_2Cl_2 (**Stock Solution B**). In 4 oven-dried 7.0 mL vials were added **3.25e** (33.4 mg, 50.2 mg, 66.9 mg, or 100.3 mg). To each oven-dried vial containing **3.25e** was added **Stock Solution A** (0.50 mL) and **Stock Solution B** (0.30 mL) to prepare the reaction samples containing different concentrations of **3.25e**. The reaction mixture was then transferred to a J-Young tube. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and ^{1}H NMR spectra were acquired in the NMR spectrometer preheated at 60 °C using a pre-acquisition delay in array mode with a spectrum taken every 22 seconds for the length of the experiment. The data were processed using MestReNova software and peak integrations were normalized using mesitylene as the internal standard.

Initial-rate kinetic analysis, which was determined based on the data points acquired in the first 600 seconds, showed that there is *–1-order dependency* on α,β-unsaturated compound **3.25e**

concentration in the reaction between **3.19t** and **3.25e** (Figures S15, 16).

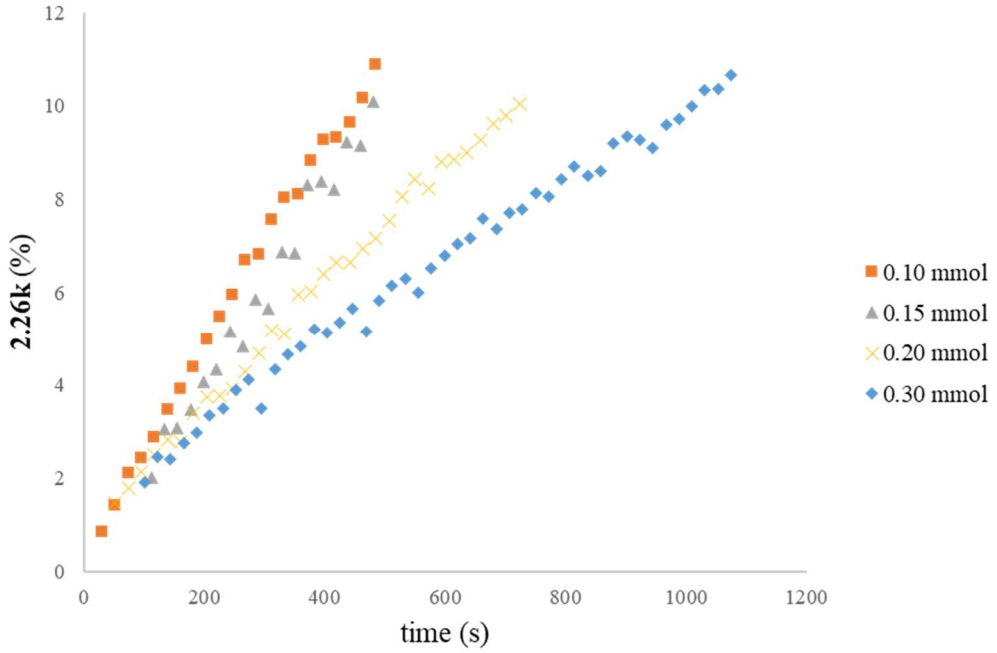


Figure S15. Monitoring the formation of **3.26k** under different concentrations of **3.25e**

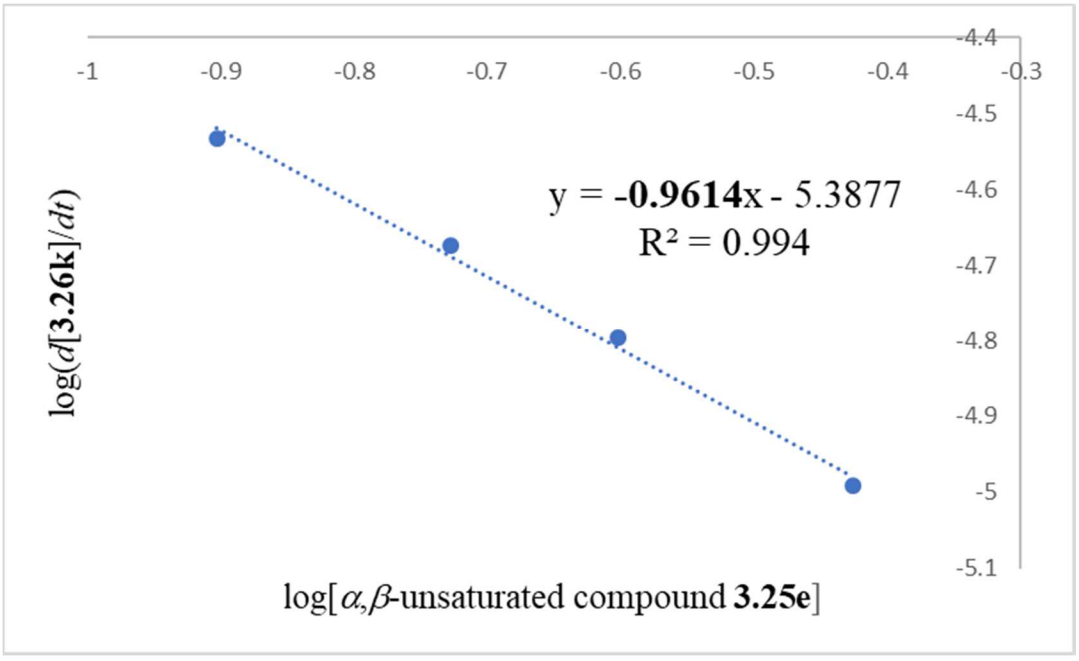


Figure S16. Log(rate) *vs* log[α,β-unsaturated compound **3.25e**] is employed to determine the initial reaction order for **3.25e**. The result suggests that there is *–1-order dependency* on **3.25e** concentration .

3.6.6.1.2. ^{19}F NMR Experiments for the Detection of the Resting State

The mechanistic investigations described above (**Section 3.6.6.1.1**) revealed that the $(F_5C_6)_3B$/**L**–Sc(OTf)$_3$ co-catalyzed β-amino C–H functionalization has a *–1 order dependency* with respect to the concentration of 1-benzyl-2-cinnamoyl-5,5-dimethylpyrazolidin-3-one **3.25e** (see **Section 3.6.6.1.4**). We hypothesized that **3.25e** and $B(C_6F_5)_3$ could form a resting state complex and therefore carried out the following ^{19}F NMR experiments to identify the structure of the complex (Figures S17, S18). Previously, the group of Piers has reported that $B(C_6F_5)_3$ and benzaldehyde forms an acid–base adduct, which gives characteristic ^{19}F NMR peaks at –135.3, –156.3, –164.5 ppm. We acquired the ^{19}F NMR spectrum of a sample containing 1:1 ratio of $B(C_6F_5)_3$ and **6g** in CD_2Cl_2 (Figures S17B, S18) and observed new ^{19}F NMR peaks at –134.8, –157.7, –164.7 ppm; based on this analysis, our spectrum is in agreement with the formation of **3.25e**–$B(C_6F_5)_3$ adduct. The resting state complex was also observed in the reaction mixture including **3.19t**, **3.25e**, $B(C_6F_5)_3$, and **L9**–Sc(OTf)$_3$ (Figure S17C).

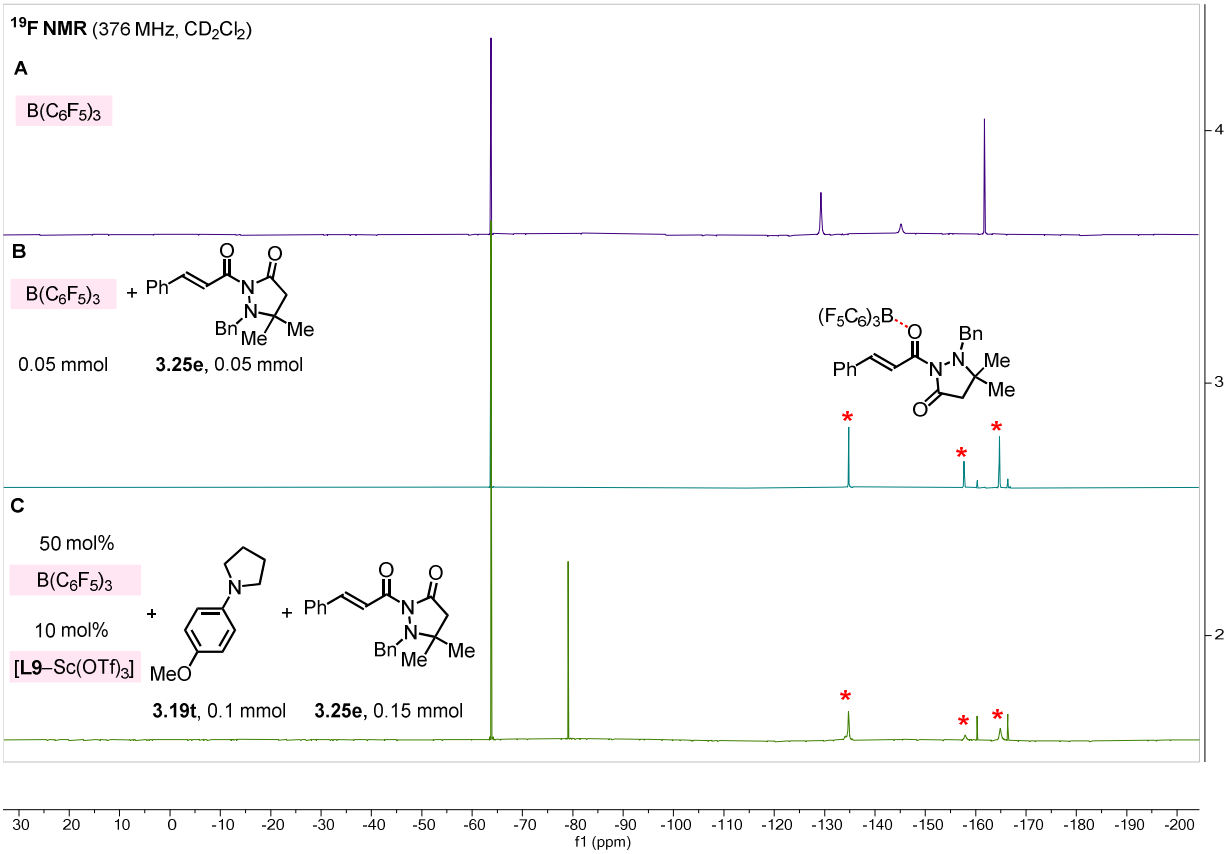


Figure S17. ^{19}F NMR experiments for the detection of the resting state

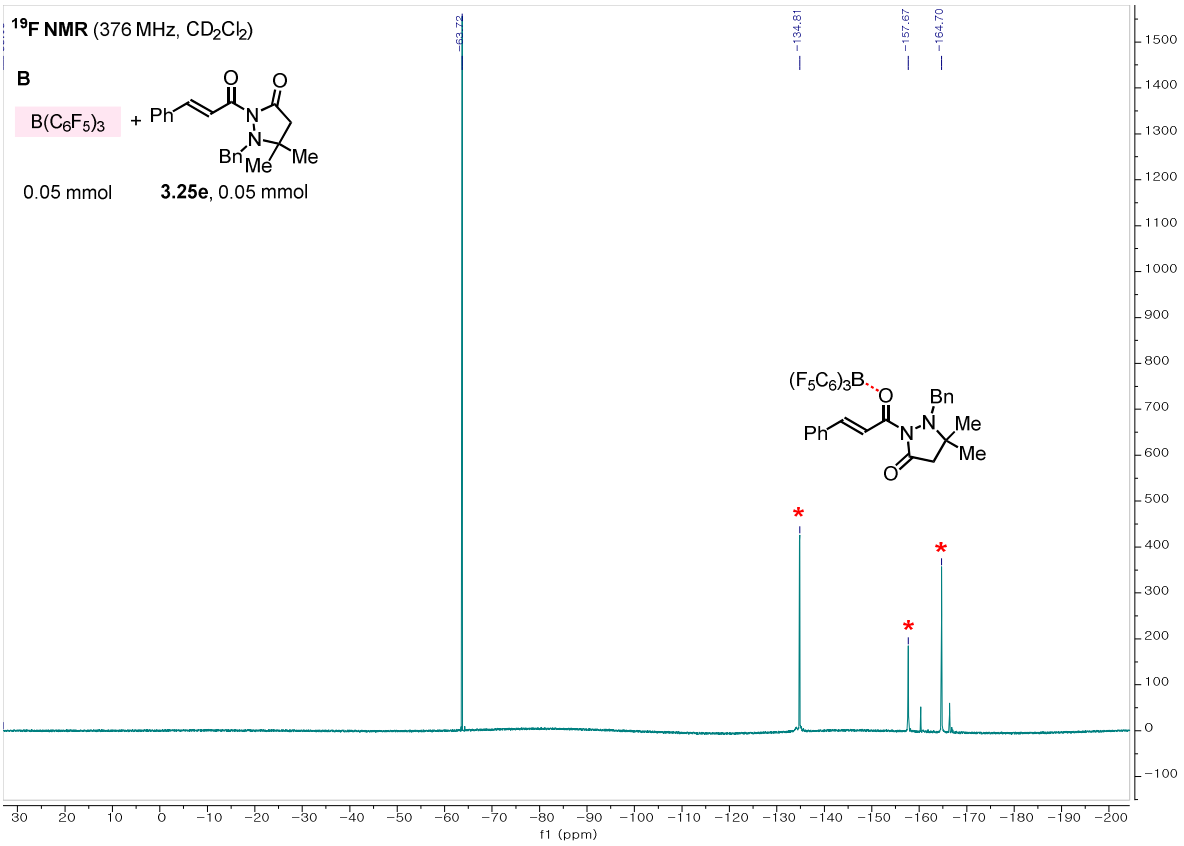


Figure S18. ^{19}F NMR spectrum of 6g–B(C_6F_5)$_3$ adduct.

3.6.6.1.3. Kinetic Isotope Effect Experiments

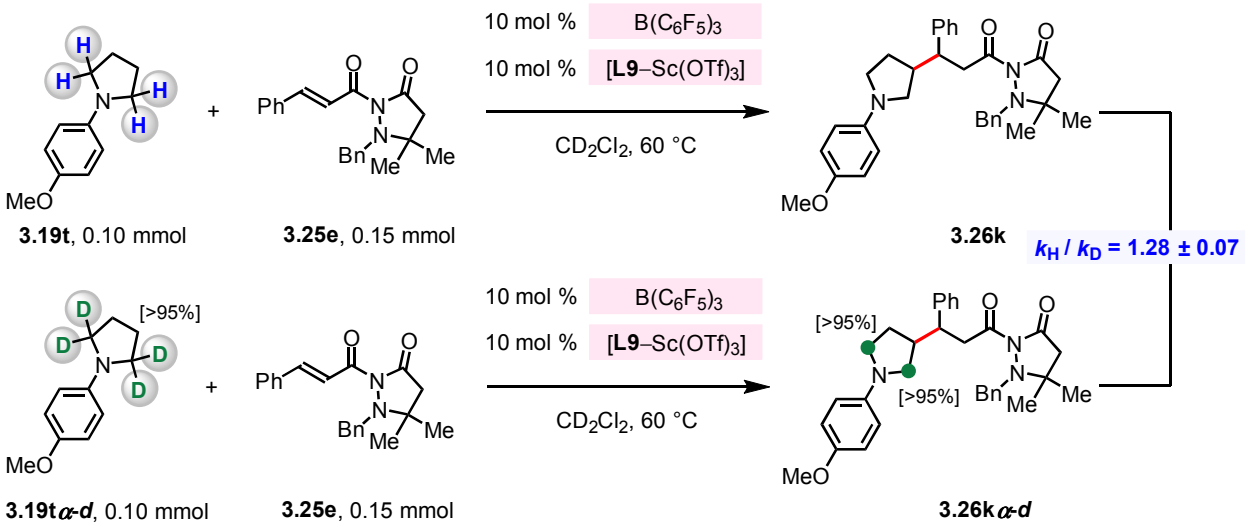
As discussed in **Section 3.6.6.1.2**, *zero-order dependency* with respect to concentration of **L9**–$Sc(OTf)_3$ suggests that enantioselective C–C bond forming reaction occurs after the turnover-limiting step. In order to probe whether the turnover-limiting step is the hydride abstraction or the deprotonation process, we carried out the following parallel kinetic isotope effect experiments.

3.6.6.1.3.1. Parallel KIE Measurement for *N*-Alkylamines Containing *α*-Amino C–H or C–D Bonds

A parallel kinetic isotope effect study was conducted through time course reaction monitoring by the ^{1}H NMR spectroscopy using internal standard to monitor the difference in initial rates of the product formation in the reaction of 1-(4-methoxyphenyl)pyrrolidine **3.19t** or 1-(4-methoxyphenyl)pyrrolidine-2,2,5,5-d_4 **3.19t*α-d*** with 1-benzyl-2-cinnamoyl-5,5-dimethylpyrazolidin-3-one **3.25e** (Scheme S16). In a nitrogen-filled glove box, $B(C_6F_5)_3$ (20.5 mg, 0.040 mmol), **L9**–$Sc(OTf)_3$ (31.6 mg, 0.040 mmol), **6g** (200.8 mg, 0.60 mmol) and mesitylene (48 mg, 0.40 mmol) were weighed in an oven-dried 7.0 mL vial and the resulting mixture was dissolved in 2.00 mL of CD_2Cl_2 (**Stock Solution A**). In two oven-dried 7.0 mL vials were added **3.19t** (20.5 mg) or **3.19t*α-d*** (20.9 mg). To each oven-dried vial containing **3.19t** or **3.19t*α-d*** was added CD_2Cl_2 (0.30 mL) and **Stock Solution A** (0.50 mL) to prepare the reaction samples containing **3.19t** or **3.19t*α-d***. The reaction mixture was then transferred to a J-Young tube. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and ^{1}H NMR spectra were acquired in the NMR spectrometer preheated at 60 °C using a pre-acquisition delay in array mode with a spectrum taken every 22 seconds for the length of the experiment. The acquired data were processed using MestReNova software and peak integrations were normalized using mesitylene as the internal standard.

From the kinetic analysis based on the initial rates of the product formation (Figure S19), KIE value of 1.28 ± 0.07 (average of two experiments) was obtained in the reaction between **3.19t** or **3.19t*α-d*** and **3.25e**. This suggests that the hydride abstraction step is not likely the turnover limiting process. From the ^{1}H NMR analysis of the isolated and purified **3.26k*α-d*** in $CDCl_3$, it was revealed that >95% of *d*-incorporation level was retained at the *α*-amino position (Figures S20–22). This result suggests that the borohydride reduction step may be irreversible as there was no H incorporation into the *α*-amino C–D bonds.

Scheme S16. Kinetic Isotope Effect Studies



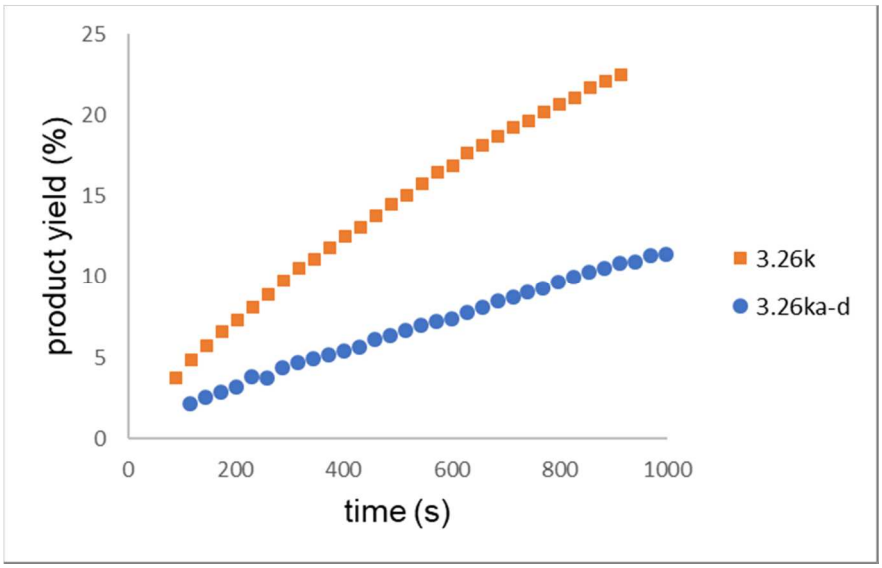


Figure S19. Monitoring the formation of products in parallel KIE measurements

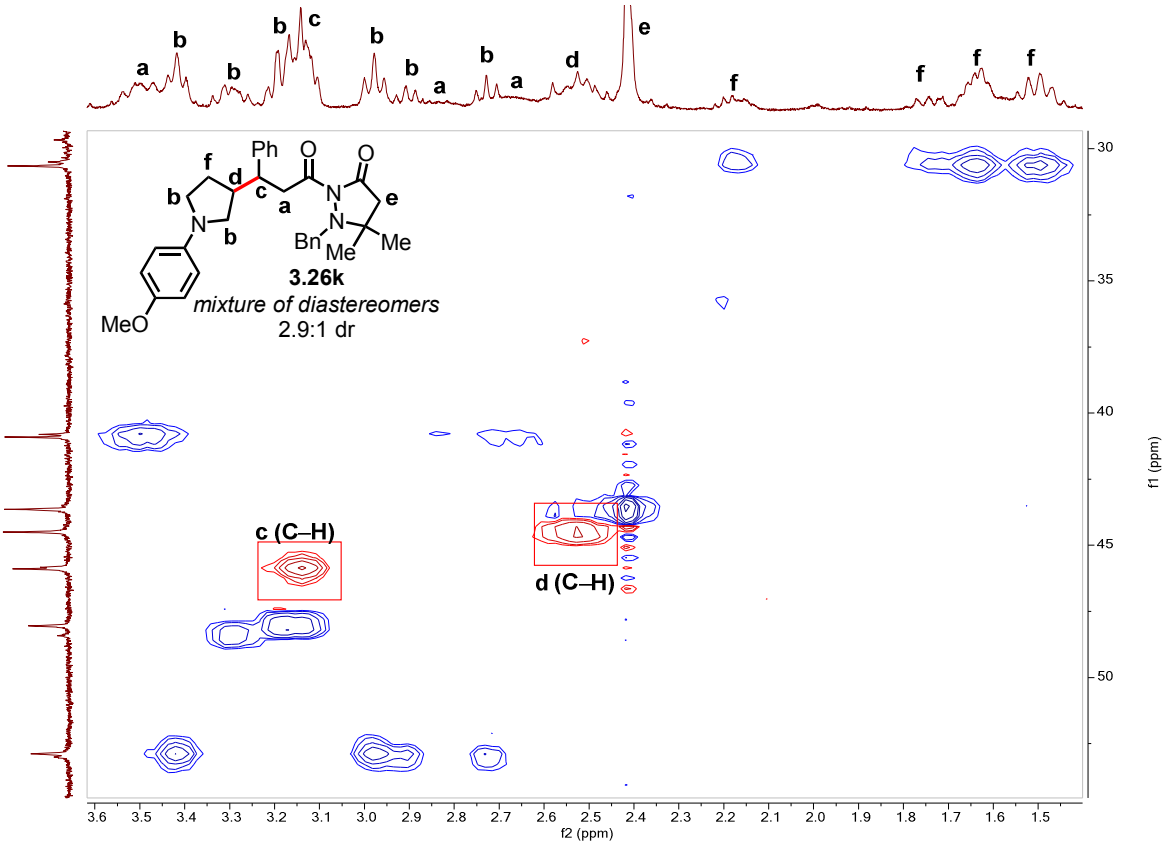


Figure S20. 2D HSQCAD spectra of **3.26k** in $CDCl_3$ (*for the assignment of the peaks*)

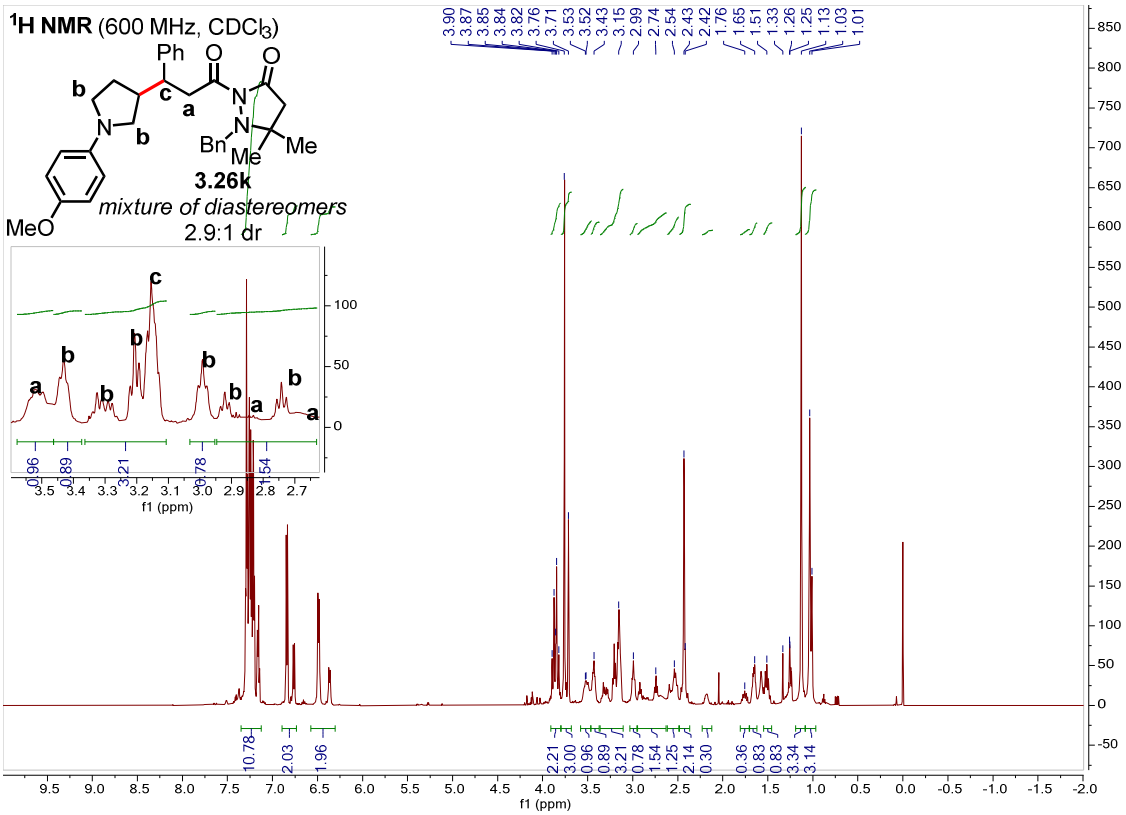


Figure S21. ^{1}H NMR spectrum of **3.26k**

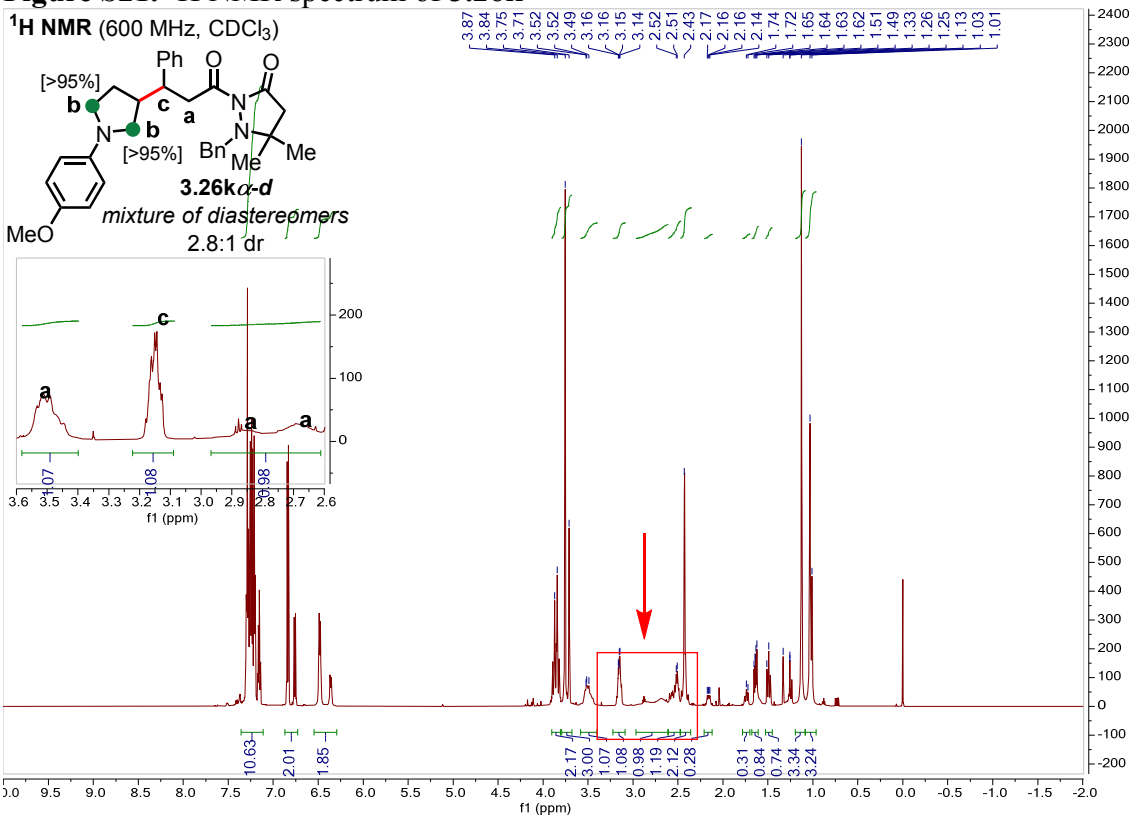


Figure S22. ^{1}H NMR spectrum of **3.26k*α-d***

3.6.6.1.3.2. Parallel KIE Measurement for *N*-Alkylamines Containing *β*-Amino C–H or C–D Bonds

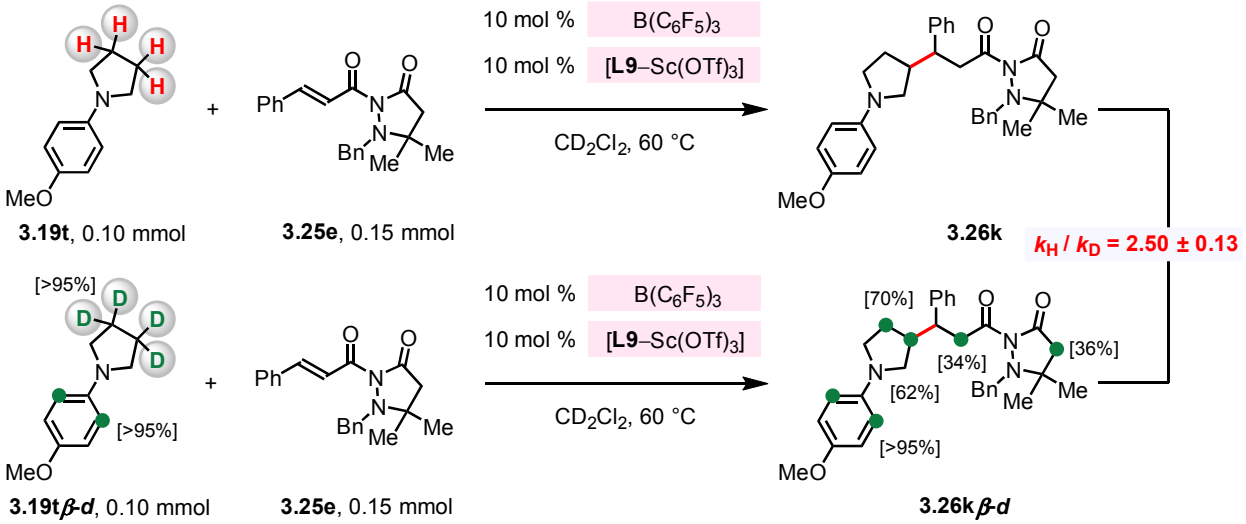
A parallel kinetic isotope effect study was conducted through time course reaction monitoring by the ^{1}H NMR spectroscopy using internal standard to monitor the difference in initial rates of the product formation in the reaction of 1-(4-methoxyphenyl)pyrrolidine **3.19t** or 1-(4-methoxyphenyl)pyrrolidine-3,3,4,4-d_4 **3.19t*β-d*** with 1-benzyl-2-cinnamoyl-5,5-dimethylpyrazolidin-3-one **3.25e** (Scheme S17). In a nitrogen-filled glove box, $B(C_6F_5)_3$ (20.5 mg, 0.040 mmol), **L9**–$Sc(OTf)_3$ (31.6 mg, 0.040 mmol), **3.25e** (200.8 mg, 0.60 mmol) and mesitylene (48 mg, 0.40 mmol) were weighed in an oven-dried 7.0 mL vial and the resulting mixture was dissolved in 2.00 mL of CD_2Cl_2 (**Stock Solution A**). In two oven-dried 7.0 mL vials were added **3.19t** (20.5 mg) or **3.19t*β-d*** (20.9 mg). To each oven-dried vial containing **3.19t** or **3.19t*β-d*** was added CD_2Cl_2 (0.30 mL) and **Stock Solution A** (0.50 mL) to prepare the reaction samples containing **3.19t** or **3.19t*β-d***. The reaction mixture was then transferred to a J-Young tube. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and ^{1}H NMR spectra were acquired in the NMR spectrometer preheated at 60 °C using a pre-acquisition delay in array mode with a spectrum taken every 22 seconds for the length of the experiment. The data were processed using MestReNova software and peak integrations were normalized using mesitylene as the internal standard.

Kinetic analysis based on the initial rates of the product formation (Figure S23) demonstrates that **3.19t** reacts 2.5 times faster than **3.19t*β-d*** ($k_H/k_D = 2.50 \pm 0.13$, average of two experiments) in the reaction between **3.19t** or **3.19t*β-d*** and **3.25e**. This result suggests that the cleavage of *β*-amino C–H bond is likely involved in the turnover-limiting step.

From the ^{1}H NMR analysis of the isolated and purified **3.26k*β-d*** in $CDCl_3$ and acetone-d_6, *d*-

incorporation level was determined (Figures S24–28). It was found that there was a *d*-scrambling between the substrates and the products at the β-amino C–H/D bonds and the α-carbonyl C–H/D bonds that are easily enolizable.

Scheme S17. Kinetic Isotope Effect Studies



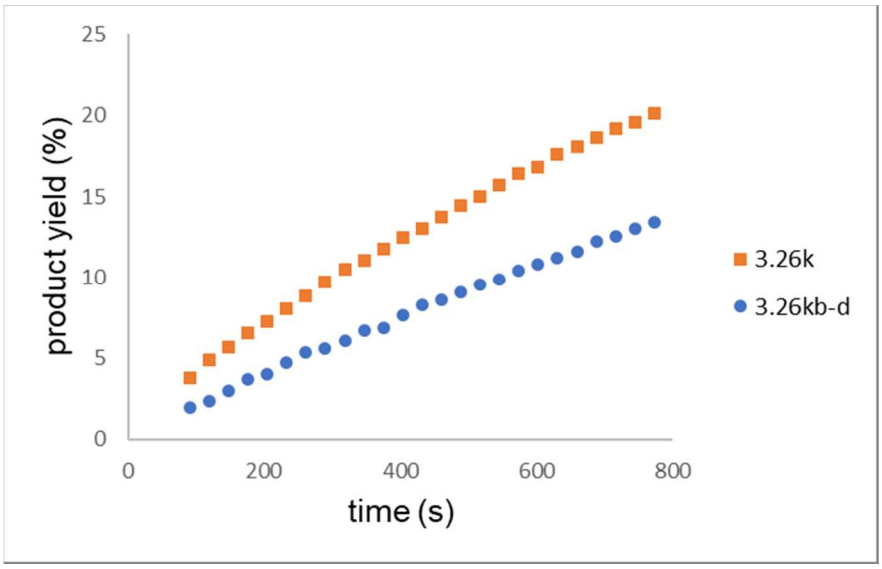


Figure S23. Monitoring the formation of products in parallel KIE measurements

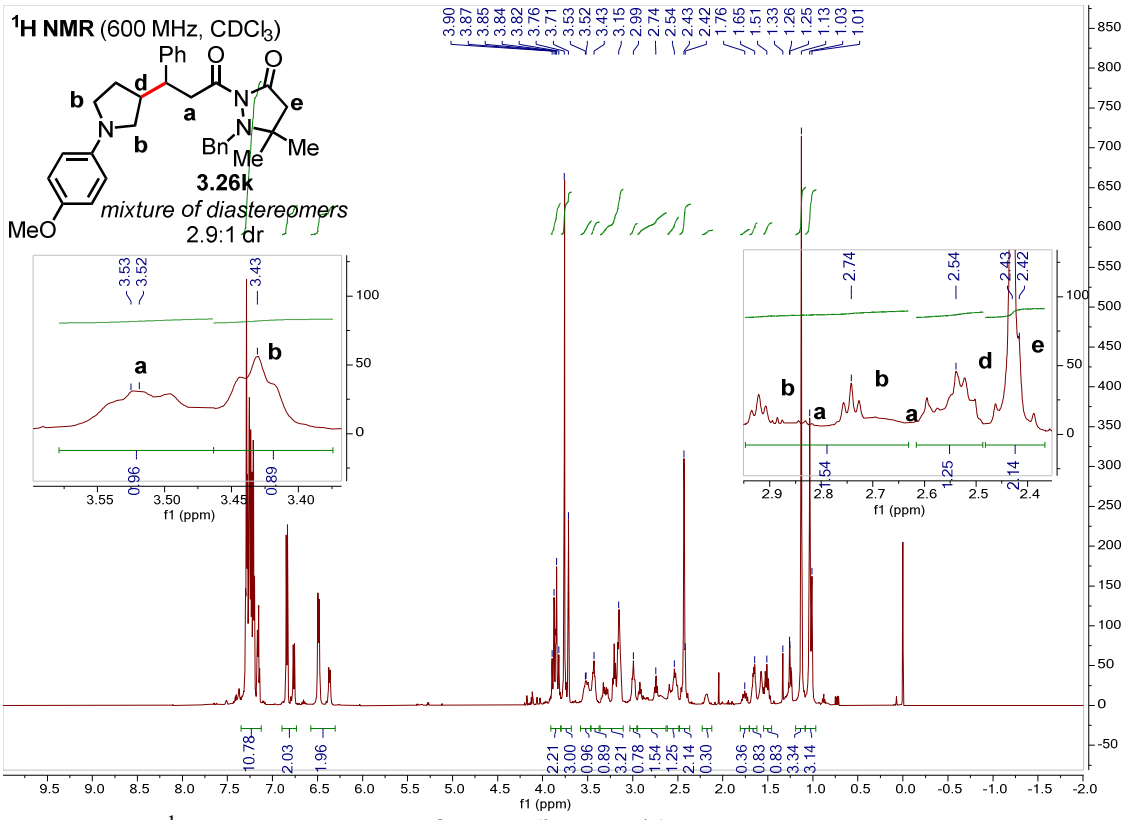


Figure S24. ^{1}H NMR spectrum of **3.26k** (in $CDCl_3$)

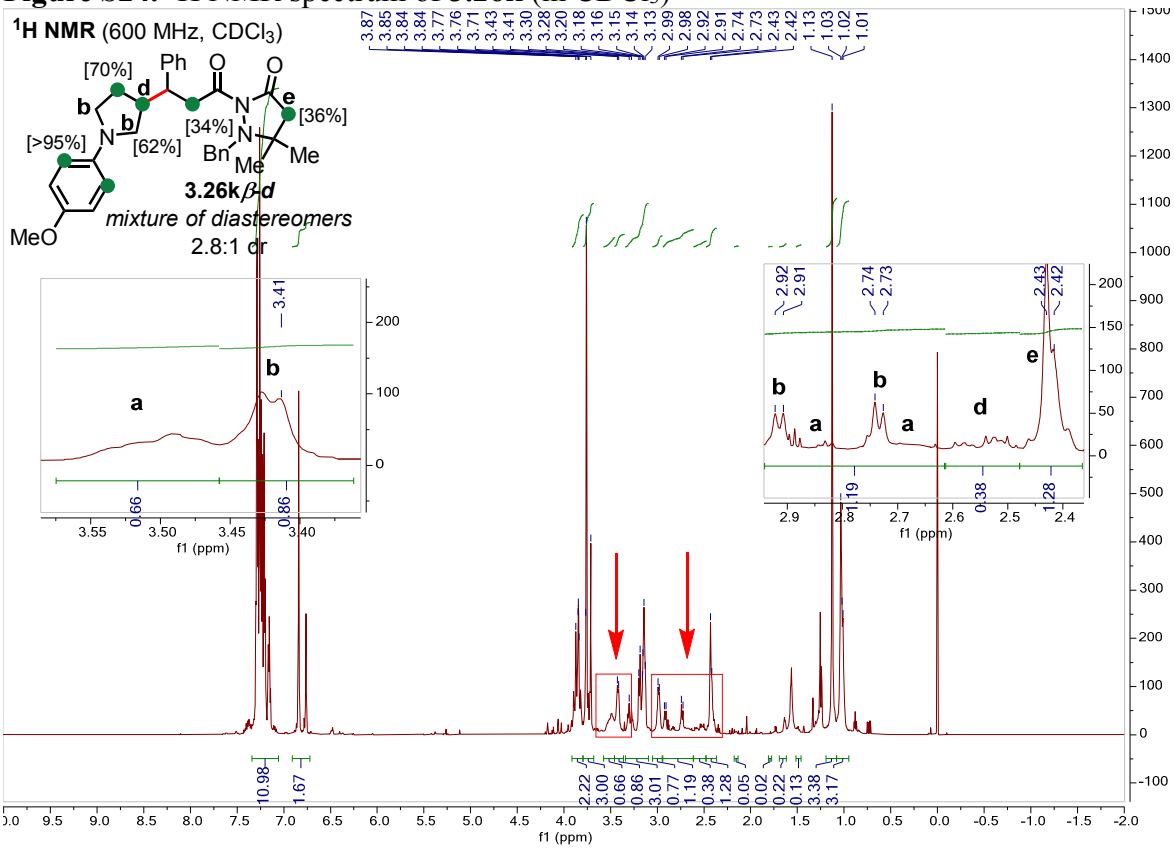


Figure S25. ^{1}H NMR spectrum of **3.26k*β-d*** (in $CDCl_3$)

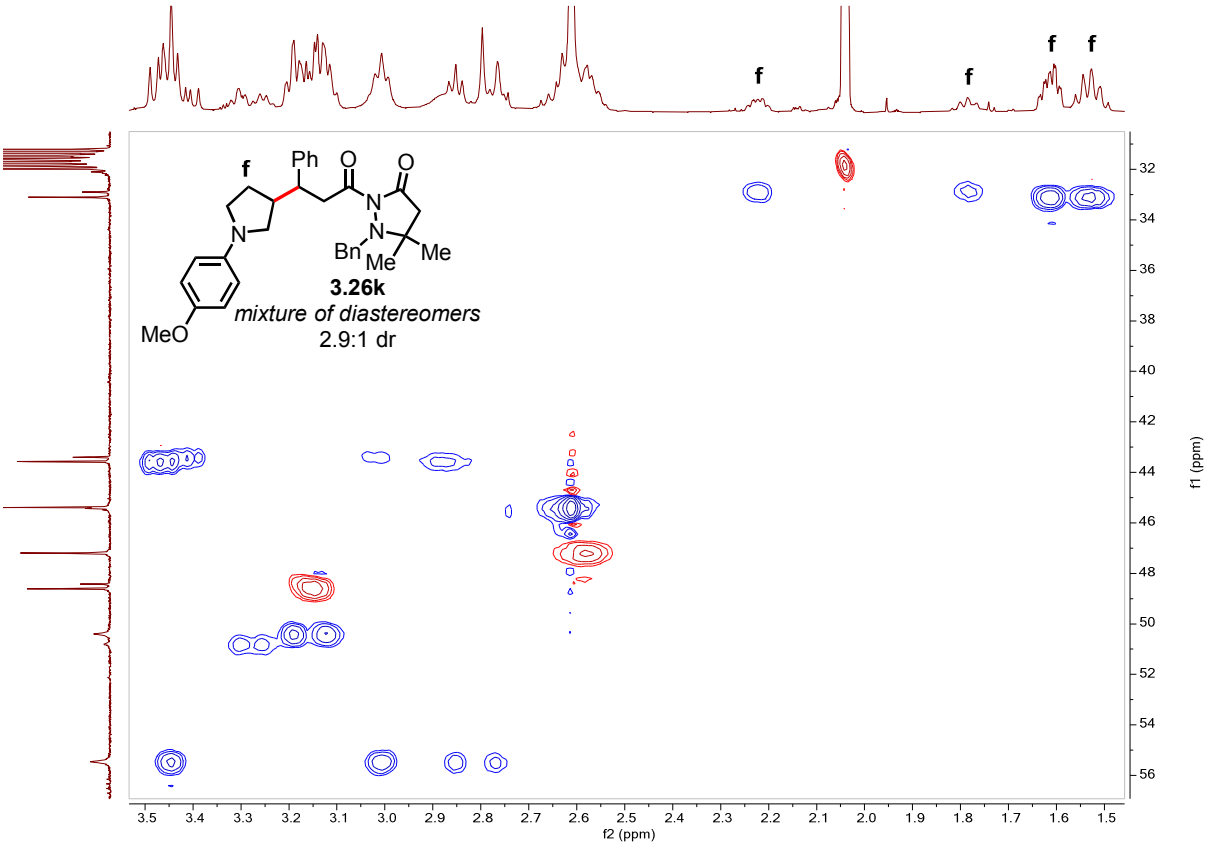


Figure S26. 2D HSQCAD spectra of **3.26k** in acetone-d_6 (*for the assignment of the peaks*)

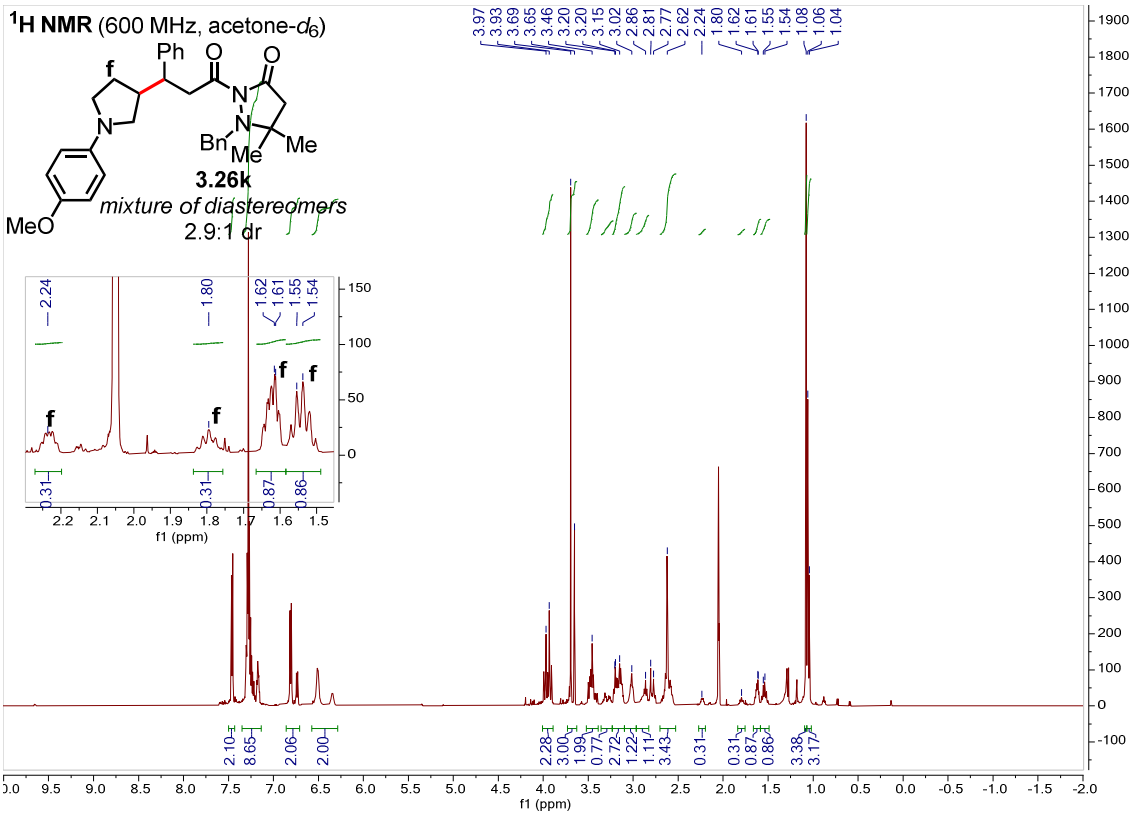


Figure S27. ^{1}H NMR spectrum of **3.26k** (in acetone-d_6)

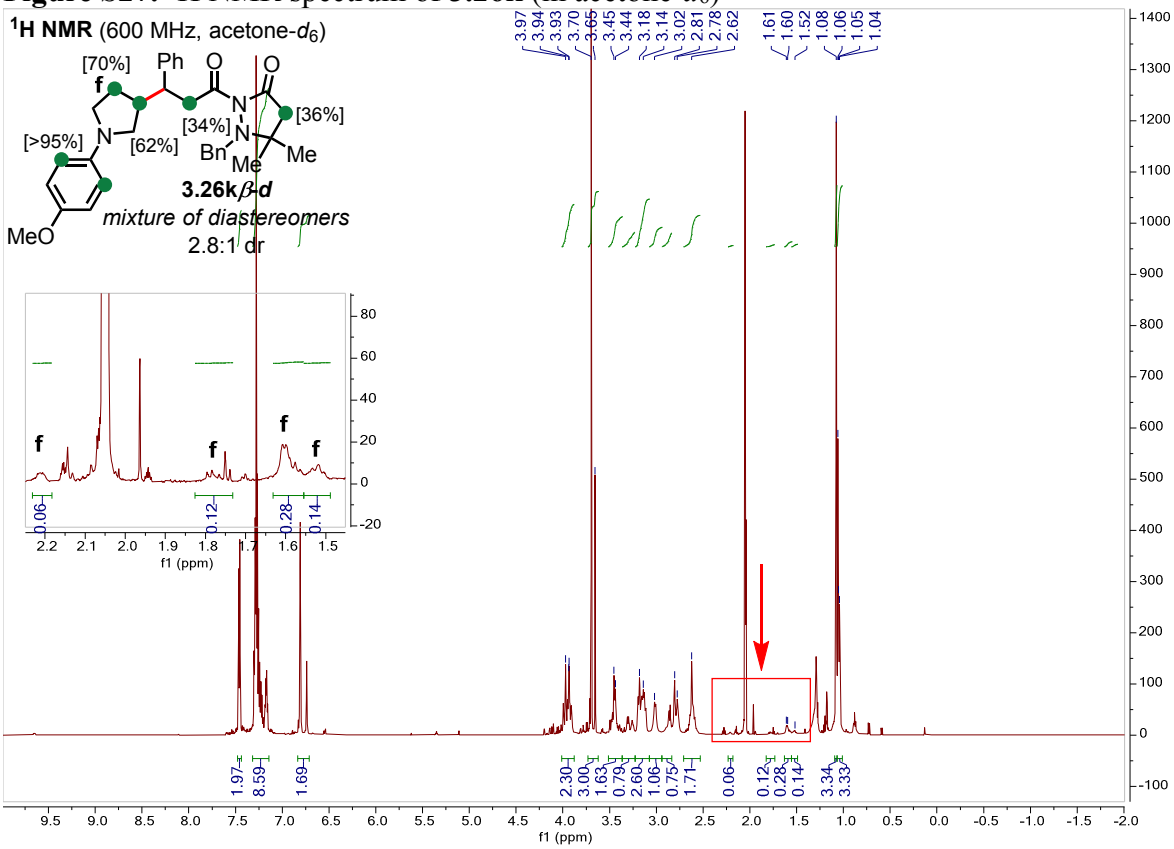


Figure S28. ^{1}H NMR spectrum of **3.26k*β-d*** (in acetone-d_6)

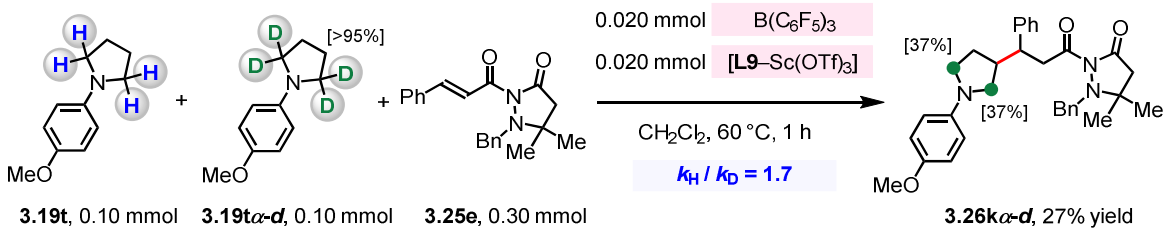
3.6.6.1.3.3. Intermolecular Competition KIE Measurement for *N*-Alkylamines Containing α-Amino C–H or C–D Bonds

In order to further probe if the turnover-limiting step is the deprotonation process, we carried out the following intermolecular competition kinetic isotope effect experiments.

An intermolecular competition kinetic isotope effect study between 1-(4-methoxyphenyl)pyrrolidine **3.19t** and 1-(4-methoxyphenyl)pyrrolidine-2,2,5,5-d_4 **3.19tα-*d*** with 1-benzyl-2-cinnamoyl-5,5-dimethylpyrazolidin-3-one **3.25e** was conducted (Scheme S18). Specifically, to a 15 mL oven-dried pressure vessel was added $B(C_6F_5)_3$ (10.2 mg, 0.020 mmol), **L9**–$Sc(OTf)_3$ (15.8 mg, 0.020 mmol), **3.25e** (100.4 mg, 0.30 mmol), **3.19t** (17.7 mg, 0.10 mmol), **3.19tα-*d*** (18.1 mg, 0.10 mmol) and DCM (1.6 mL) under nitrogen atmosphere. The mixture was placed in an oil bath at 60 °C and was allowed to stir for 1 hour. Upon completion, the solution was cooled to 22 °C and concentrated *in vacuo.* The ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that product **3.26kα-*d*** was obtained in 27% yield (3.5:1 dr). After purification by column chromatography (EtOAc:hexanes = 1:3), **3.26kα-*d*** was obtained as a light yellow liquid.

From the ^{1}H NMR analysis of the isolated and purified **3.26kα-*d*** in $CDCl_3$ (Figures S29, S30), KIE value of 1.7 was obtained in the reaction between **3.19t** and **3.26kα-*d*** with **3.25e**. This result is in line with the previous independent kinetic isotope effect studies and supports that the hydride abstraction step is not likely the turnover limiting process.

Scheme S18. Kinetic Isotope Effect Studies



3.19t, 0.10 mmol **3.19t*α*-*d***, 0.10 mmol **3.25e**, 0.30 mmol **3.26k*α*-*d***, 27% yield

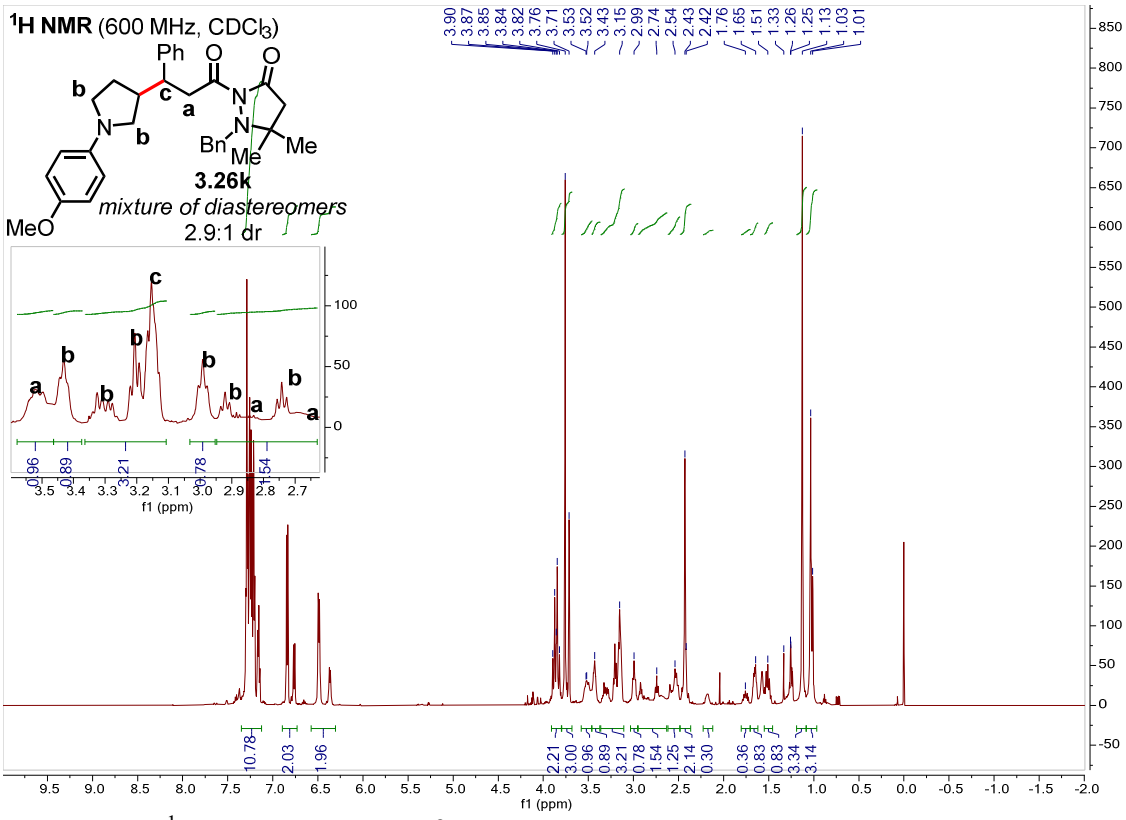


Figure S29. ^{1}H NMR spectrum of **3.26k**

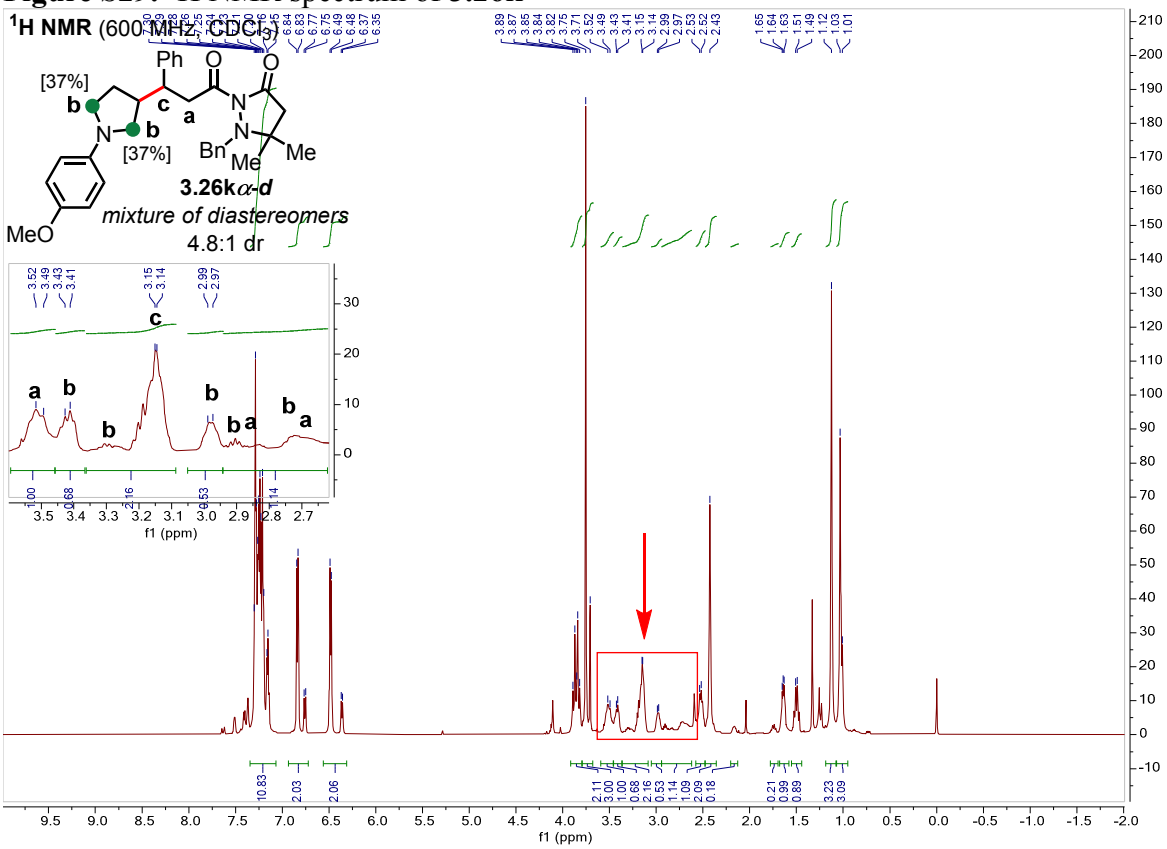


Figure S30. ^{1}H NMR spectrum of **3.26k*α-d***

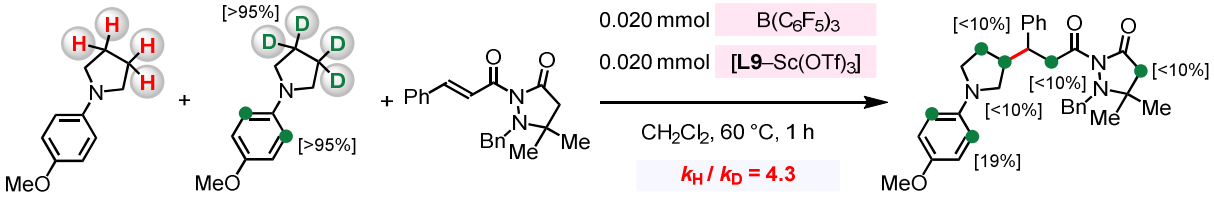
3.6.6.1.3.4. Intermolecular Competition KIE Measurement for *N*-Alkylamines Containing *β*-Amino C–H or C–D Bonds

An intermolecular competition kinetic isotope effect study between 1-(4-methoxyphenyl)pyrrolidine **13.19t** and 1-(4-methoxyphenyl)pyrrolidine-3,3,4,4-d_4 **3.19t*β-d*** with 1-benzyl-2-cinnamoyl-5,5-dimethylpyrazolidin-3-one **3.25e** was conducted (Scheme S19). Specifically, to a 15 mL oven-dried pressure vessel was added $B(C_6F_5)_3$ (10.2 mg, 0.020 mmol), **L9**–$Sc(OTf)_3$ (15.8 mg, 0.020 mmol), **6g** (100.4 mg, 0.30 mmol), **3.19t** (17.7 mg, 0.10 mmol), **3.19t*β-d*** (18.1 mg, 0.10 mmol) and DCM (1.6 mL) under nitrogen atmosphere. The mixture was placed in an oil bath at 60 °C and was allowed to stir for 1 hour. Upon completion, the solution was cooled to 22 °C and concentrated *in vacuo.* The ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that product **3.26k*β-d*** was obtained in 23% yield (2.0:1 dr). After purification by column chromatography (EtOAc:hexanes = 1:3), **3.26k*β-d*** was obtained as a light yellow liquid.

From the ^{1}H NMR analysis of the isolated and purified **3.26k*β-d*** in $CDCl_3$ (Figures S31, S32), it was found that **3.19t** reacts 4.3 times faster than **3.19t*β-d*** (k_H/k_D = 4.3) in the reaction between **3.19t** or **3.19t*β-d*** and **3.26k*β-d***. This result is in line with the previous independent kinetic isotope effect studies and supports that the cleavage of *β*-amino C–H bond is likely involved in the turnover-limiting step.

It was found that there was a *d*-scrambling between the substrates and the products at the *β*-amino C–H/D bonds and the *α*-carbonyl C–H/D bonds that are easily enolizable.

Scheme S19. Kinetic Isotope Effect Studies



3.19t, 0.10 mmol **3.19t*β-d***, 0.10 mmol **3.25e**, 0.30 mmol **3.26k*β-d***, 23% yield

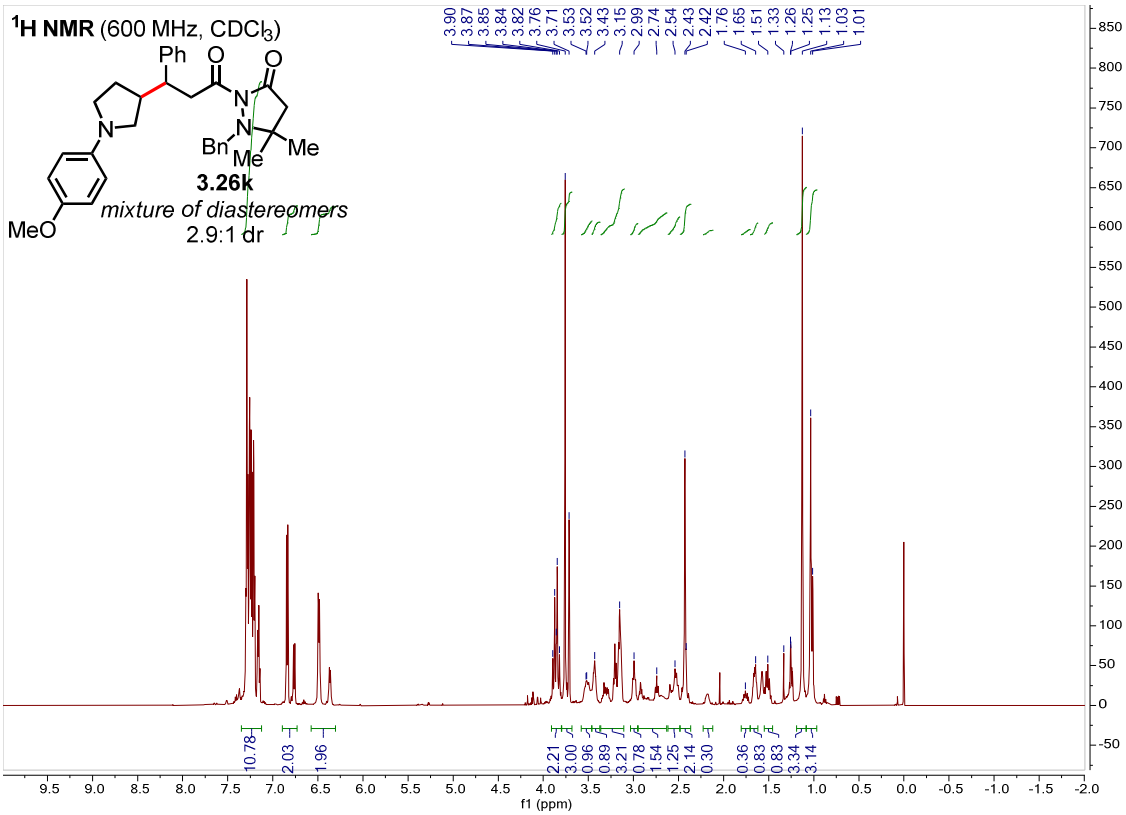


Figure S31. ^{1}H NMR spectrum of **3.26k** (in $CDCl_3$)

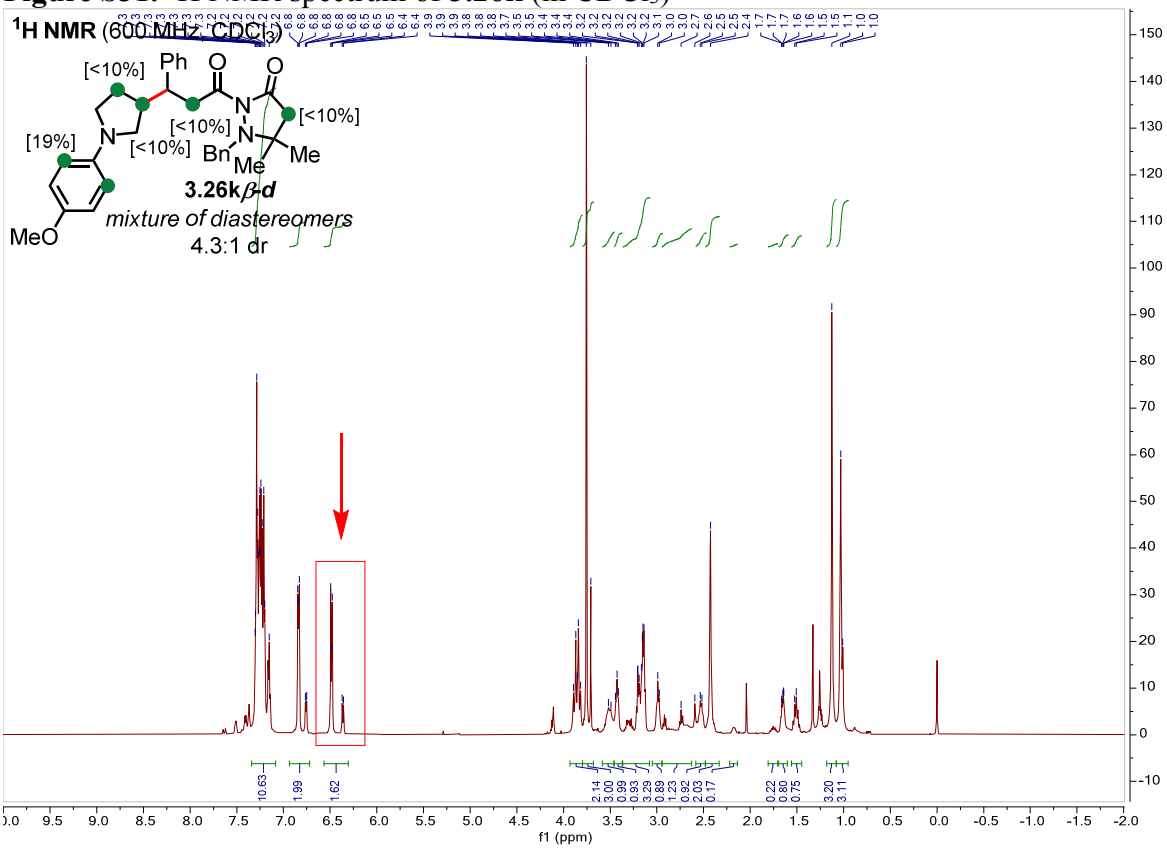


Figure S32. ^{1}H NMR spectrum of **3.26k*β-d*** (in $CDCl_3$)

3.6.6.1.4. Hammett Studies

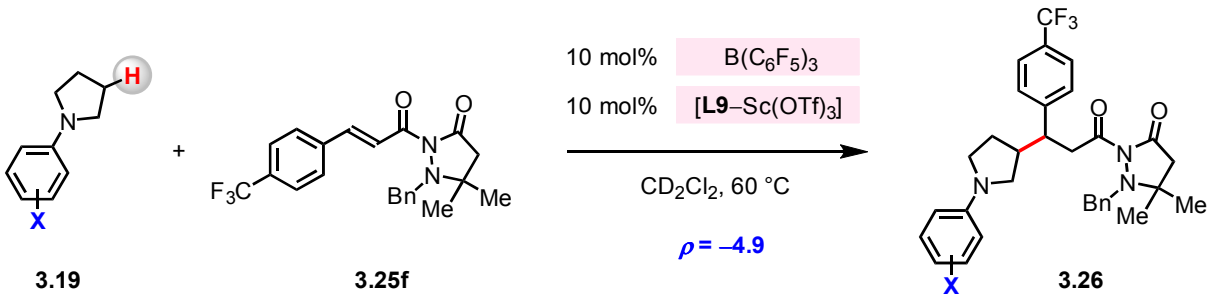
In order to study the effect of varying the substituents on aryl groups of *N*-alkylamine as well as α,β-unsaturated substrates on the rate of C–H alkylation, we carried out the following Hammett studies.

3.6.6.1.4.1 Determination of the Hammett ρ Value for *N*-Aryl Substituted Pyrrolidines

A Hammett ρ value for the reaction of *N*-aryl substituted pyrrolidines (**3.19t**, **3.19w–3.19y**) and (*E*)-1-benzyl-5,5-dimethyl-2-(3-(4-(trifluoromethyl)phenyl)acryloyl)pyrazolidin-3-one **3.25f** was determined by time course reaction monitoring by the ^{1}H NMR spectroscopy using mesitylene as an internal standard. In a nitrogen-filled glove box, **L9**–$Sc(OTf)_3$ (39.5 mg, 0.050 mmol), **3.25f** (302 mg, 0.75 mmol), mesitylene (60 mg, 0.50 mmol), and C_6F_6 (46.5 mg, 0.25 mmol) were weighed in an oven-dried 7.0 mL vial and the resulting mixture was dissolved in 2.00 mL of CD_2Cl_2 (**Stock Solution A**). In another oven-dried 7.0 mL vial, $B(C_6F_5)_3$ (30.7 mg, 0.060 mmol) was weighed and dissolved in 1.20 mL of CD_2Cl_2 (**Stock Solution B**). In 4 oven-dried 7.0 mL vials, were added 0.10 mmol of each amine. To each oven-dried vial containing amine was added **Stock Solution A** (0.40 mL), **Stock Solution B** (0.20 mL), and CD_2Cl_2 (0.20 mL) to prepare the reaction samples containing amines **3.19t**, **3.19w**, **3.19x**, or **3.19y**. The reaction mixture was then transferred to a J-Young tube. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and the ^{1}H NMR spectra were acquired in the NMR spectrometer preheated at 60 °C using a pre-acquisition delay in array mode with a spectrum taken every 22 seconds for the length of the experiment. The data were processed using MestReNova software and peak integrations were normalized using mesitylene as the internal standard.

The large negative ρ value (–4.9) obtained implies the development of positive charge at the reaction center in the transition state at or prior to the turnover-limiting step. This result thereby

supports the proposed mechanism (see **section 3.6.6.2**) in which $B(C_6F_5)_3$ abstracts a hydride from *N*-arylpyrrolidine to form an *N*-aryl iminium cation, and its isomerization into a positively charged enammonium species; both processes take place at or prior to the turnover-limiting step (Figure S33).



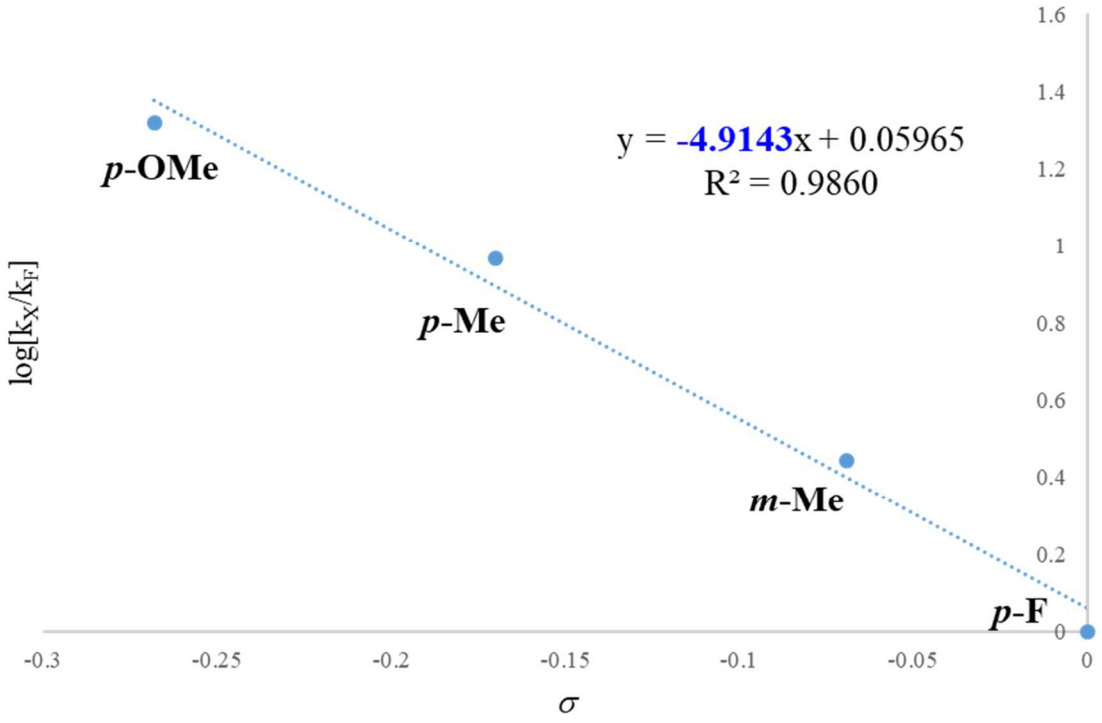


Figure S33. Log(k_X/k_F) *vs* σ is employed to determine the ρ value

3.6.6.1.4.2. Determination of the Hammett ρ Value for Aryl Substituted α,β-Unsaturated Compounds

A Hammett ρ value for the reaction of 1-(4-methoxyphenyl)pyrrolidine (**3.19t**) and aryl substituted α,β-unsaturated compounds (**3.25e–3.25h**) was determined by time course reaction monitoring by the ^{1}H NMR spectroscopy using mesitylene as an internal standard. In a nitrogen-filled glove box, **L9**–Sc(OTf)$_3$ (39.5 mg, 0.050 mmol), **3.19t** (88.5 mg, 0.50 mmol), and mesitylene (60 mg, 0.50 mmol) were weighed in an oven-dried 7.0 mL vial and the resulting mixture was dissolved in 2.00 mL of CD_2Cl_2 (**Stock Solution A**). In another oven-dried 7.0 mL vial, $B(C_6F_5)_3$ (30.7 mg, 0.060 mmol) was weighed and dissolved in 1.20 mL of CD_2Cl_2 (**Stock Solution B**). In 4 oven-dried 7.0 mL vials, were added 0.15 mmol of each α,β-unsaturated compounds **3.25**. To each oven-dried vial containing amine was added **Stock Solution A** (0.40 mL), **Stock Solution B** (0.20 mL), and CD_2Cl_2 (0.20 mL) to prepare the reaction samples containing α,β-unsaturated compounds **3.25e**, **3.25f**, **3.25g**, or **3.25h**. The reaction mixture was then transferred to a J-Young tube. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and the ^{1}H NMR spectra were acquired in the NMR spectrometer preheated at 60 °C using a pre-acquisition delay in array mode with a spectrum taken every 22 seconds for the length of the experiment. The data were processed using MestReNova software and peak integrations were normalized using mesitylene as the internal standard.

The σ^+ was used in the Hammett plot since the electron-donating ability of the *p*-OMe substituent was enhanced through conjugation in the α,β-unsaturated compound **3.25**. The positive ρ value (0.92) obtained implies the development of negative charge at the reaction center in the transition state at or prior to the turnover-limiting step. This result thereby supports the mechanistic hypothesis (see **section 3.6.6.2**) that **3.25** reacts with in situ generated $[(F_5C_6)_3B–H]^-$ to afford a

negatively charged boron–enolate intermediate, and that this hydride transfer occurs at or prior to the turnover-limiting step (Figure S34).

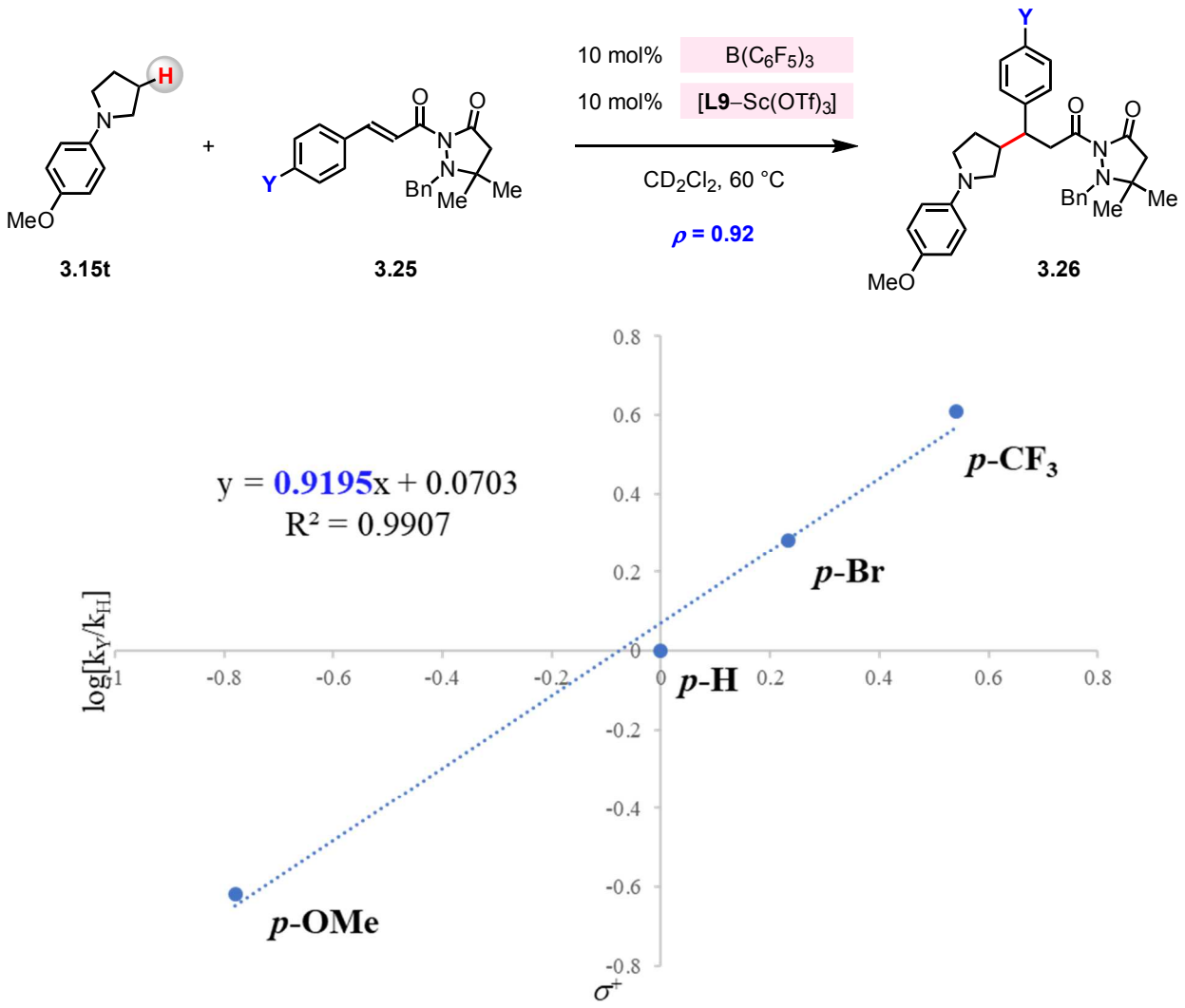


Figure S34. Log(k_Y/k_H) *vs* σ^+ is employed to determine the ρ value

3.6.6.2. Catalytic Cycle Consistent with the Results of Mechanistic Studies

Based on the kinetic studies as described above (**Section 3.6.6.1**), we propose the following catalytic cycle (Figure S35). *Zero-order dependency* with respect to concentration of **L9**–$Sc(OTf)_3$ suggests that enantioselective C–C bond forming reaction between in situ generated enamine and [**L9**–$Sc(OTf)_3$]-activated **3.25e** (**XXVII** → **XXVIII,** Figure S35) occurs after the turnover-limiting step (see **Section 3.6.6.1.1.2**). *–1-Order dependency* on the concentration of **3.25e** suggests that the transformation has a resting state of **3.25e**–$B(C_6F_5)_3$ adduct (**XXIII**), which was suggested by ^{19}F NMR studies (see **Sections 3.6.6.1.1.4, 3.6.6.1.2**). Kinetic isotope effect studies demonstrate that cleavage of β-amino C–H bond is likely the turnover-limiting step (see **Section 3.6.6.1.3**). The large negative ρ value (-4.9) obtained from Hammett study of *N*-aryl substituted pyrrolidines supports the proposed mechanism that $(F_5C_6)_3B$-catalyzed hydride abstraction to generate *N*-aryl iminium cation, and its isomerization into an enammonium species taking place at or prior to the turnover-limiting step (see **Section 3.6.6.1.4**).

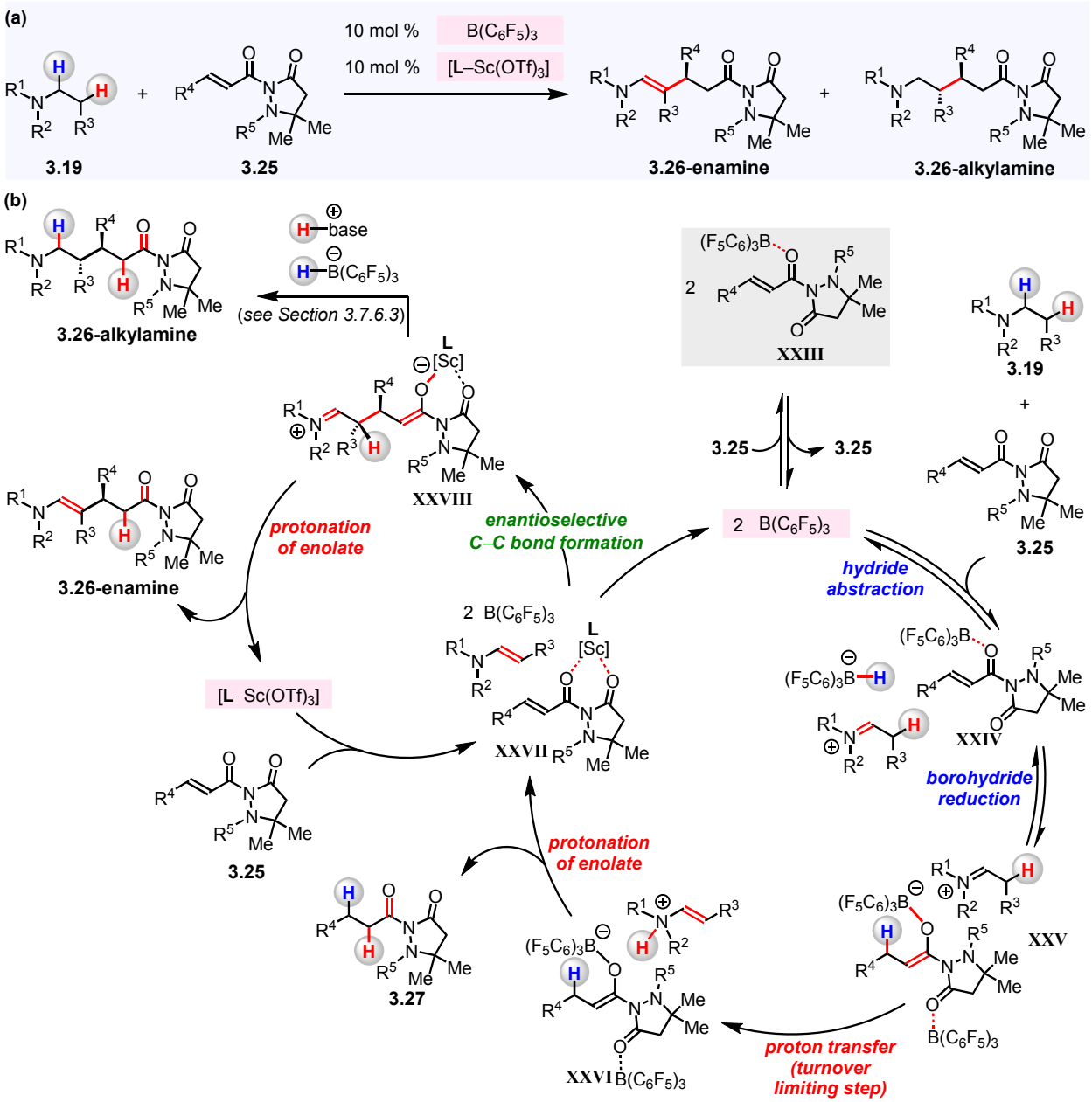


Figure S35. A catalytic cycle consistent with the results of the mechanistic investigation

3.6.6.3. Origin of Enamine and *N*-Alkylamine Products

In the *β*-amino C–H alkylation process, the products were obtained either as **3.26-enamine**, **3.26-alkylamine**, or a mixture of the two (Figure S35). We questioned if the *N*-alkylamine products were formed through transfer hydrogenation of **XXVIII** (**XXVIII→ 3.26-alkylamine**). Alternatively, **3.26-alkylamine** could be generated through reduction of **3.26-enamine** (**XXVIII → 3.26-enamine → 3.26-alkylamine**). In order to understand the origin of **3.26-enamine** and **3.26-alkylamine** products, we conducted the following experiments.

Section 3.6.6.3.1: Kinetic Profile for the *β*-Alkylation of *N*-Arylpiperidine

Section 3.6.6.3.2: Transfer Hydrogenation of Compound **3.21v**

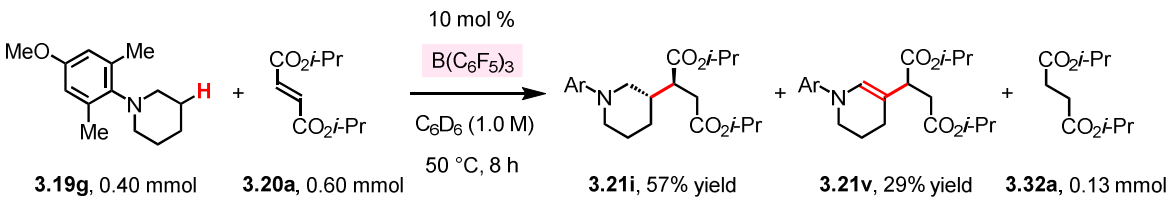
Section 3.6.6.3.3: Dehydrogenation of Compound **3.21i**

3.6.6.3.1. Kinetic Profile for the *β*-Alkylation of *N*-Arylpiperidine

As shown in Scheme 3.16 in the manuscript, the reaction of *N*-arylpiperidine **3.19g** and diisopropylfumarate **3.20a** with 10 mol% $B(C_6F_5)_3$ in benzene (1.0 M) was found to give *N*-alkylamine **3.21i** and enamine **3.21v** in 57% yield and 29% yield, respectively. Since the products were obtained as a mixture of **3.21i** and **3.21v**, it would be a good platform to study whether the *N*-alkylamine and enamine products are interconvertible. To determine if **3.21i** can be generated by $(F_5C_6)_3B$-catalyzed transfer hydrogenation of **3.21v**, we monitored the progress of this reaction by the ^1H NMR spectroscopy (Figure S36). To an oven-dried 7.0 mL vial, amine **3.19g** (88 mg, 0.40 mmol), diisopropyl fumarate **3.25a** (120 mg, 0.60 mmol), mesitylene (48 mg, 0.40 mmol), $B(C_6F_5)_3$ (10 mol%) and 0.4 mL C_6D_6 were added under nitrogen atmosphere. Then, the reaction mixture was transferred to a J-Young tube which was tightly capped with the Teflon plug and taken

out of the glove box. The ^{1}H NMR spectra were acquired in the NMR spectrometer preheated at 50 °C using a pre-acquisition delay in array mode with a spectrum taken every 22 seconds for the length of the experiment. The data were processed using MestReNova software and peak integrations were normalized using *m*-xylene as the internal standard.

As shown in Figure S36, it was found that there was minimal transformation of **3.21v** into **3.21i**, evidenced by the mostly unchanged concentration of **3.21v** once >85% of amine **3.19g** was consumed (after ca. 100 minutes).



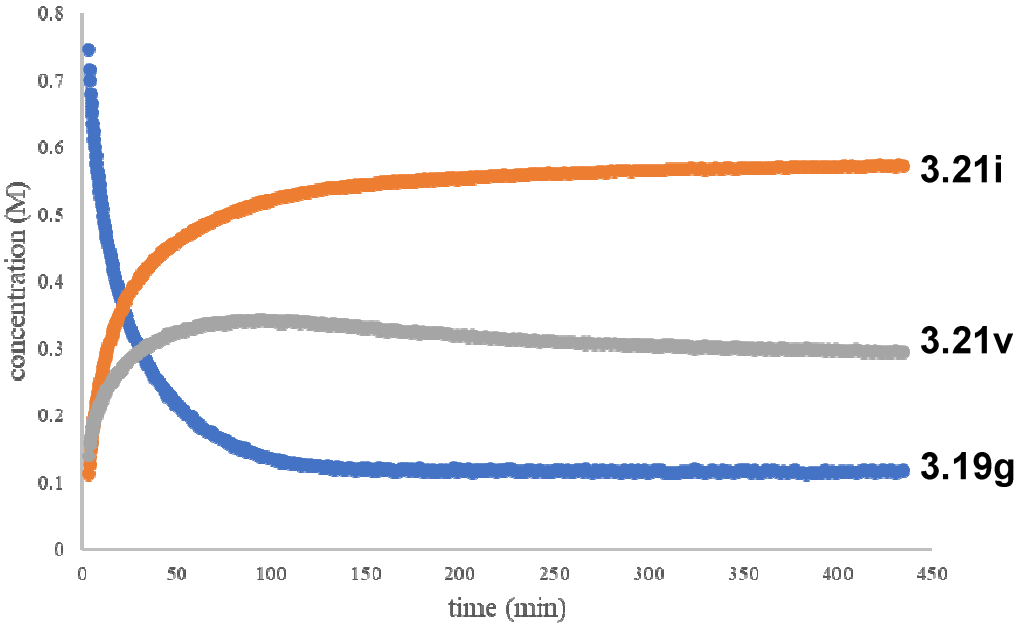


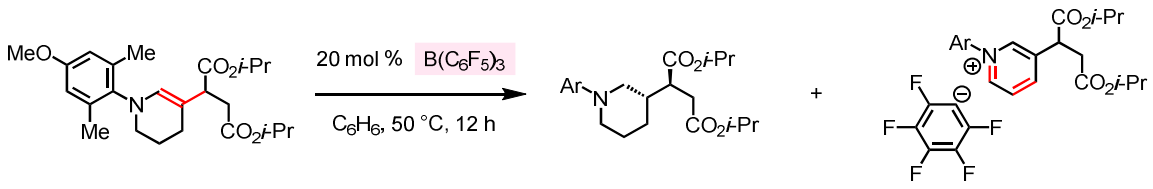
Figure S36. Progress of the reaction between **3.19g** and **3.20a**

3.6.6.3.2 Transfer Hydrogenation of Compound 3.21v

As shown in Scheme 3.16 in the manuscript, transfer hydrogenation of compound **3.21v** (Figure S14, S15) was conducted to further probe whether the enamine product can be reduced to generate the *N*-alkylamine product **3.21i**.

To a 15 mL oven-dried pressure vessel, **3.21v** (0.050 mmol), $B(C_6F_5)_3$ (20 mol%) and benzene (0.20 mL) were added under a nitrogen atmosphere (Scheme S20). The reaction mixture was placed in an oil bath at 50 °C for 12 hours. Upon completion, the solution was cooled to 22 °C and concentrated *in vacuo*. Through the ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard, it was found that **3.21i** was formed in 30% yield, together with an ionic complex of $[pyridinium]^+[C_6F_5]^-$ (**3.33**) which was generated in 15% yield. This experiment implies that enamine **3.21v** can serve as H^+/H^- source in $(F_5C_6)_3B$-catalyzed transfer hydrogenation of **3.21v** to afford *N*-alkylamine product **3.21i**.

Scheme S20. Transfer Hydrogenation Studies involving Compound **3.21v**



3.21v, 0.05 mmol **3.21i**, 30% yield **3.33**, 15% yield

3-(1,4-Diisopropoxy-1,4-dioxobutan-2-yl)-1-(4-methoxy-2,6-dimethylphenyl)pyridin-1-ium perfluorobenzen-1-ide (3.33)

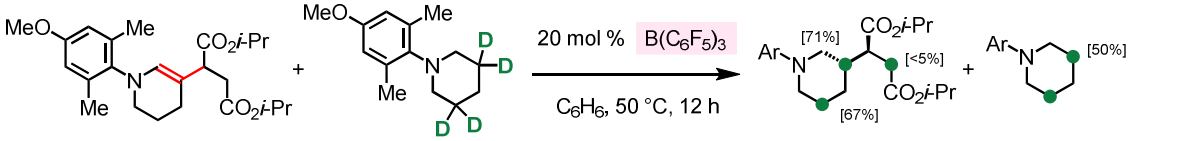
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.60 (d, *J* = 8.2 Hz, 1H), 8.37 (dd, *J* = 6.0, 1.3 Hz, 1H), 8.13 – 8.08 (m, 1H), 6.80 (d, *J* = 4.2 Hz, 2H), 5.06 (dt, *J* = 12.2, 6.5 Hz, 1H), 4.88 (p, *J* = 6.7 Hz, 1H), 4.26 (dd, *J* = 8.7, 4.8 Hz, 1H), 3.87 (s, 3H), 3.10 (dd, *J* = 18.1, 4.9 Hz, 1H), 3.03 (dd, *J* =

17.7, 8.7 Hz, 1H), 1.97 (s, 3H), 1.94 (s, 3H), 1.26 (d, *J* = 5.1 Hz, 3H), 1.21 (d, *J* = 5.7 Hz, 3H), 1.18 (d, *J* = 6.2 Hz, 3H), 1.14 (d, *J* = 6.2 Hz, 3H); **^{19}F NMR (564 MHz, $CDCl_3$):** δ -137.48 (d, *J* = 23.9 Hz), -160.45 (t, *J* = 20.1 Hz), -165.00 (t, *J* = 19.4 Hz); **HRMS (DART):** Calcd for $C_{30}H_{33}F_5NO_5$ (MH^+): 582.2273; found: 582.2253.

$(F_5C_6)_3B$-catalyzed transfer hydrogenation of enamines was previously reported by Stephan and co-workers; 1-(1-cyclohexen-1-yl)-piperidine was reduced to afford 1-cyclohexylpiperidine in the presence of 20 mol% $B(C_6F_5)_3$ and large excess of $(i\text{-Pr})_2NH$ (the mixture was allowed to stir at 100 °C for 24 hours).[30] In our transformation (Figure 2), amine substrate **3.19g** may serve as H^+/H^- source in transfer hydrogenation of **3.21v**. To determine if this is possible, to a 15 mL oven-dried pressure vessel were added enamine **3.21v** (0.050 mmol), amine **3.19g-*d*** (0.05 mmol, 1.0 equiv), $B(C_6F_5)_3$ (20 mol%) and benzene (0.20 mL) under a nitrogen atmosphere (Scheme S21). The reaction mixture was placed in an oil bath at 50 °C for 12 hours. Upon completion, the solution was cooled to 22 °C and concentrated *in vacuo*. Through the ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard, it was found that **3.21i-*d*** was formed in 50% yield with <5% of **3.33** formation when 58% of **3.19g-*d*** was recovered. Furthermore, deuterium incorporation level was determined after the isolation and purification of **3.21i-*d*** and **3.19g-*d*,** which revealed that there was *d*-scrambling at the *β*-position of **3.19g-*d*** and **3.21i-*d*** (see 1.6–2.0 ppm in Figures S37, S38) when there was no significant deuterium incorporation at the *β*-amino position of recovered **3.21v**. These results imply that amine **3.19g-*d*** can serve as D^+ and H^- source in $(F_5C_6)_3B$-catalyzed transfer hydrogenation of **3.21v** to afford *N*-alkylamine product **3.21i-*d***.

[30] Farrell, J. M.; Heiden, Z. M.; Stephan, D. W. *Organometallics* **2011**, *30*, 4497–4500.

Scheme S21. Transfer Hydrogenation Studies involving Compound **3.21v**



3.21v, 0.05 mmol **3.19g-*d***, 0.05 mmol **3.21i-*d***, 50% yield **3.19g-*d***, 58% recovered

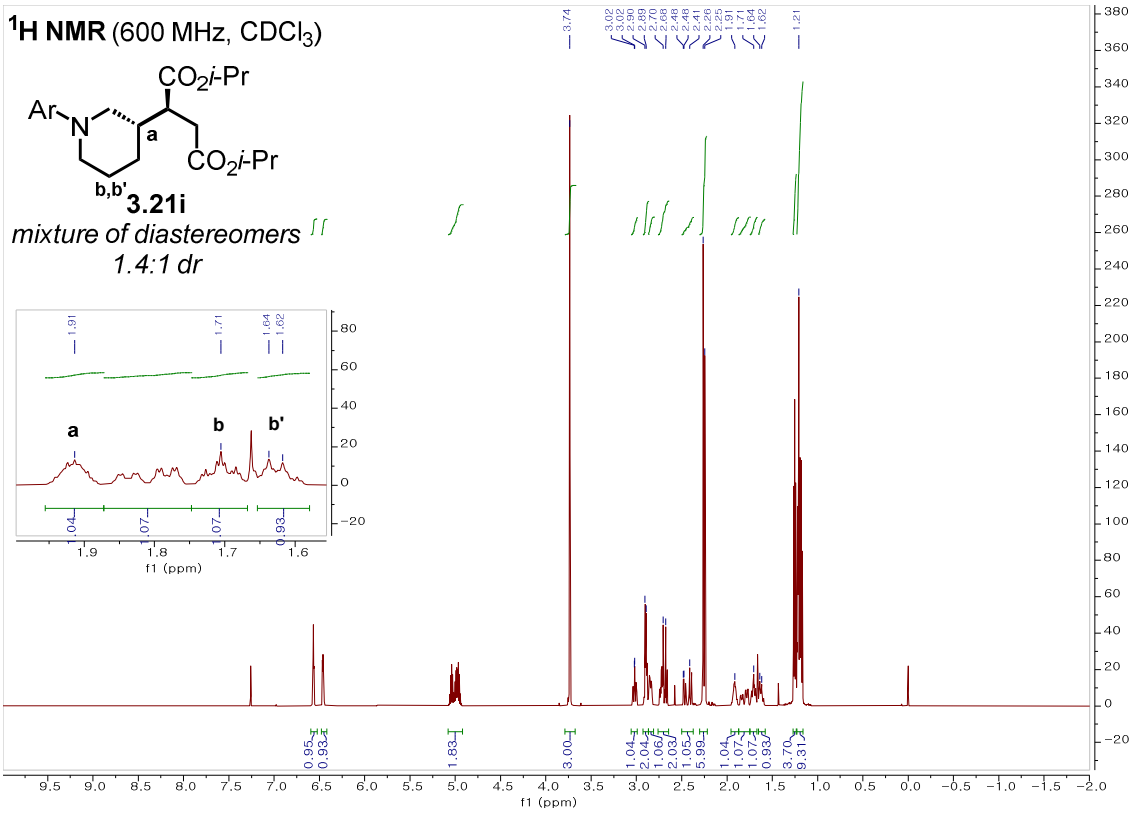


Figure S37. ^{1}H NMR Spectrum of **3.21i**

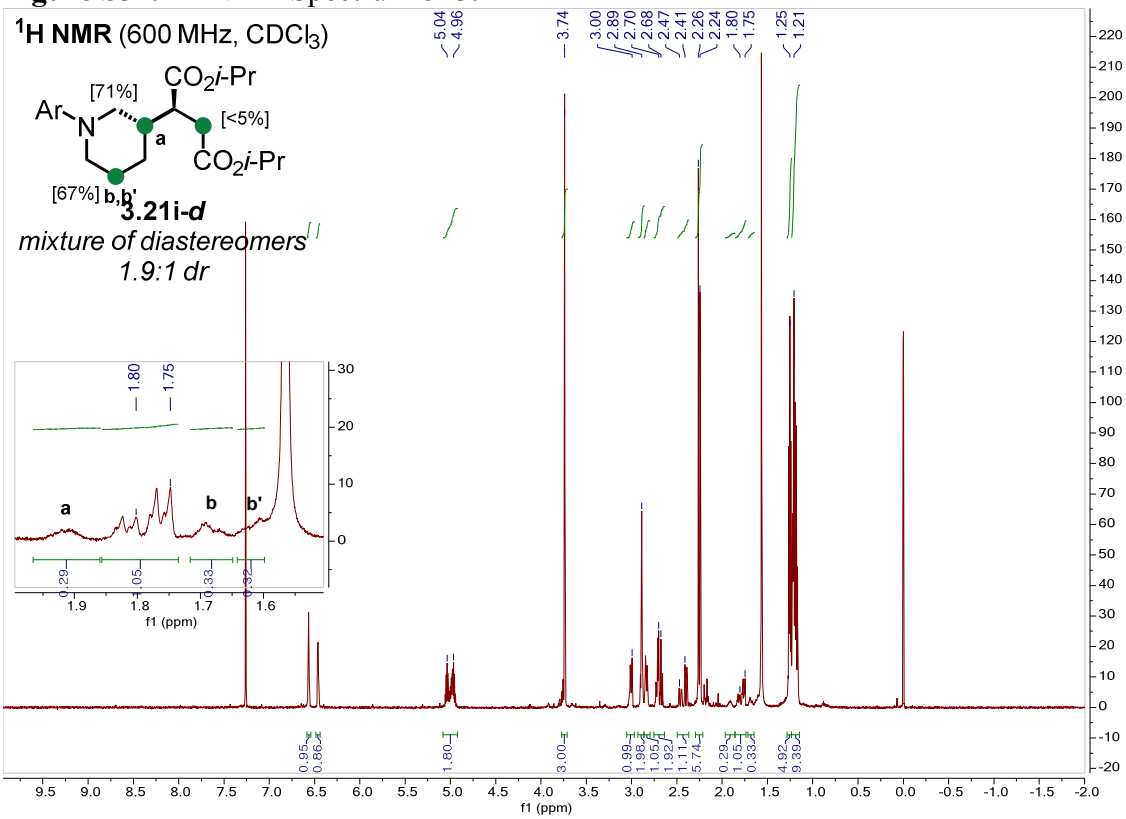


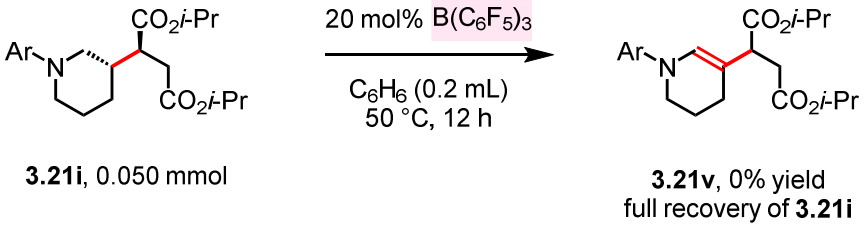
Figure S38. ^{1}H NMR Spectrum of **3.21i-*d***

3.6.6.3.3. Dehydrogenation of Compound 3.21i

As discussed in the **Sections 3.6.6.3.1–3.6.6.3.2**, under the standard reaction conditions, *N*-alkylamine **3.21i** is likely generated by transfer hydrogenation of **XXVIII** (Figure S35) without the intermediacy of enamine **3.21v**. In order to probe whether enamine **3.21v** can be generated from *N*-alkylamine **3.21i** through oxidation, dehydrogenation of compound **3.21i** (Scheme S22-23) was conducted.

To a 15 mL oven-dried pressure vessel was added amine **3.21i** (21 mg, 0.050 mmol), $B(C_6F_5)_3$ (20 mol%) and benzene (0.20 mL) under a nitrogen atmosphere (Scheme S22). The reaction mixture was placed in an oil bath at 50 °C and was allowed to stir for 12 hours. Upon completion, the reaction mixture was cooled to 22 °C and concentrated *in vacuo*. Through the ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard, it was found that **3.21i** was fully recovered and formation of **3.21v** was not observed.

Scheme S22. Dehydrogenation Studies involving Compound **3.21i**

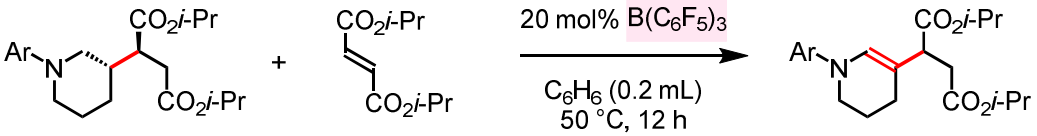


3.21i, 0.050 mmol

3.21v, 0% yield
full recovery of **3.21i**

We hypothesized that in order to obtain enamine **3.21v**, the presence of diisopropylfumarate **3.20a** might be necessary to serve as a H^+/H^- acceptor. Therefore, **3.20a** (10 mg, 0.05 mmol, 1.0 equiv.) was added to the reaction mixture of amine **3.21i** (21 mg, 0.05 mmol), $B(C_6F_5)_3$ (20 mol%) and benzene (0.2 mL) under a nitrogen atmosphere (Scheme S23). The reaction mixture was placed in an oil bath at 50 °C and was allowed to stir for 12 hours. Upon completion, the reaction mixture was cooled to 22 °C and concentrated *in vacuo*. However, after ^1H NMR analysis of the unpurified product mixture using mesitylene as the internal standard, formation of **3.21v** was not observed. These experiments revealed that **3.21i** cannot be readily converted to **3.21v** by $B(C_6F_5)_3$, regardless of whether α,β-unsaturated compound **3.20a** is present in the reaction mixture or not. This result implies that **3.21v** is generated from the deprotonation of **XXVIII** (Figure S35), not through the oxidation of **3.21i**. Therefore, the interconversion between **3.21i** and **3.21v** under the standard reaction conditions is unlikely to take place.

Scheme S23. Dehydrogenation Studies involving Compound **3.21i**



3.21i, 0.050 mmol **3.20a**, 0.050 mmol **3.21v**, 0% yield

3.6.6.4 Mechanistic Studies Involving Ester Substituted α,β-Unsaturated Compound 3.25a

We performed mechanistic investigations on the reaction between *N*-alkylamine **3.19t** and ethyl ester-substituted electrophile **3.25a** to probe if the mechanism of β-C–H alkylation may be different depending on which electrophile is used (vs the processes involving aryl-substituted electrophiles in **Section 3.6.6.1** to **3.6.6.3**).

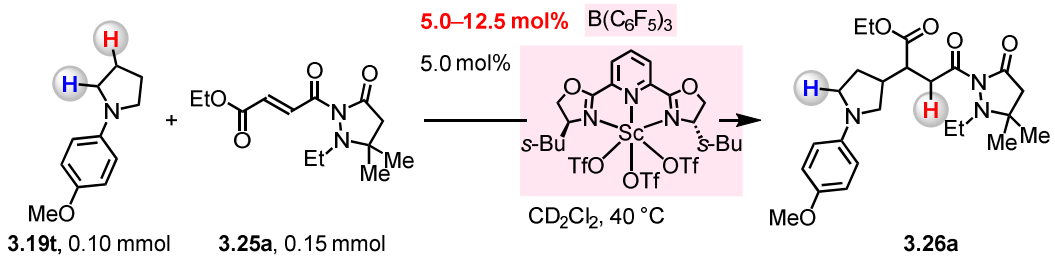
3.6.6.4.1. Determination of the Reaction Orders Involving 3.25a

For the β-C–H alkylation reaction involving 1-(4-methoxyphenyl)pyrrolidine **3.19t** and **3.25a**, the reaction order of each reactant was studied through time course reaction monitoring by the ^{1}H NMR spectroscopic analysis.

3.6.6.4.1.1. Reaction Order of $B(C_6F_5)_3$

The reaction between **3.19t** and **3.25a** was performed using different concentrations of $B(C_6F_5)_3$ and the progress of each reaction was monitored by the ^{1}H NMR spectroscopy (Scheme S24).

Scheme S24. Determination of the Reaction Order of $B(C_6F_5)_3$



In a nitrogen-filled glove box, **L12**–$Sc(OTf)_3$ (24.6 mg, 10 mol%), **3.19t** (106.2 mg, 0.60 mmol), **3.25a** (241.2 mg, 1.5 equiv) and toluene (55.2 mg, 1.0 equiv) were weighed in an oven-dried 7.0 mL vial and the resulting mixture was dissolved in 2.40 mL of CD_2Cl_2 (**Stock Solution A**). In another oven-dried 7.0 mL vial, $B(C_6F_5)_3$ (35.8 mg, 0.070 mmol) was weighed and dissolved in 1.40 mL of CD_2Cl_2 (**Stock Solution B**). To each J-Young tube was added **Stock Solution A** (0.40 mL), **Stock Solution B** (0.10, 0.15, 0.20, or 0.25 mL) and CD_2Cl_2 (0.30, 0.25, 0.20, or 0.15 mL)

to prepare the reaction samples containing different concentrations of $B(C_6F_5)_3$. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and the ^1H NMR spectra were acquired in the NMR spectrometer preheated at 40 °C using a pre-acquisition delay in array mode with a spectrum taken every 22 seconds for the length of the experiment. The data were processed using MestReNova software and peak integrations were normalized using toluene as the internal standard.

Initial-rate kinetic analysis, which was determined based on the data points acquired in the first 600 seconds, showed that there is *fourth-order dependency* on $B(C_6F_5)_3$ concentration in the reaction between **3.19t** and **3.25a** (Figures S39, S40).

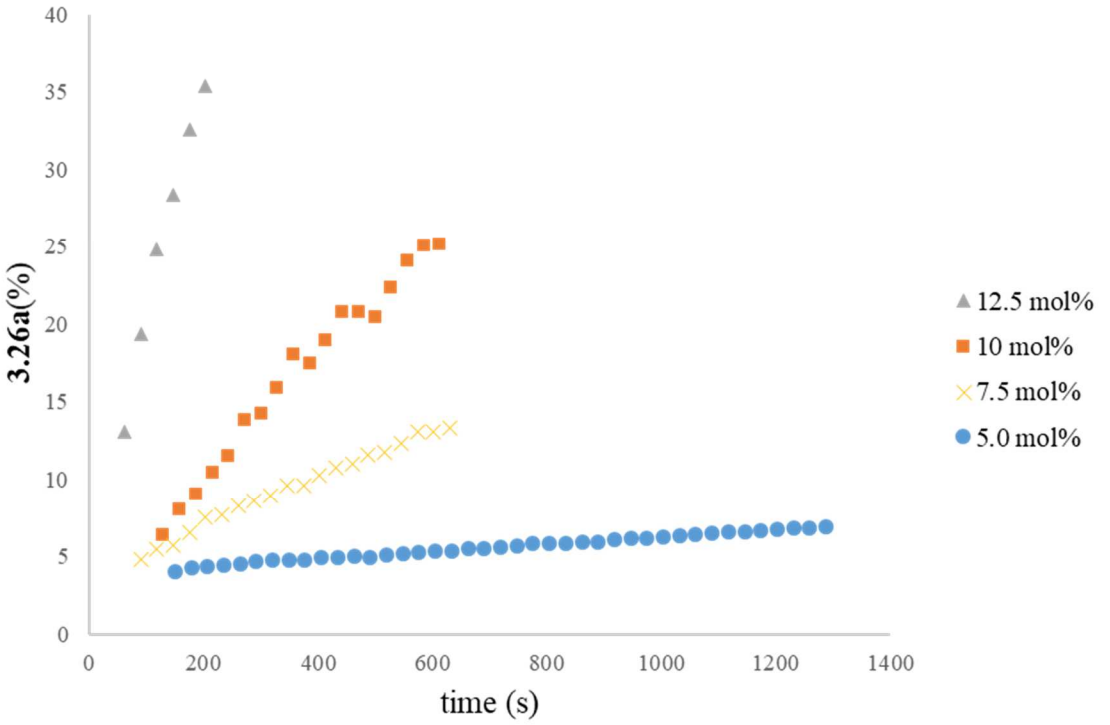


Figure S39. Monitoring the formation of **3.26a** under different concentrations of $B(C_6F_5)_3$

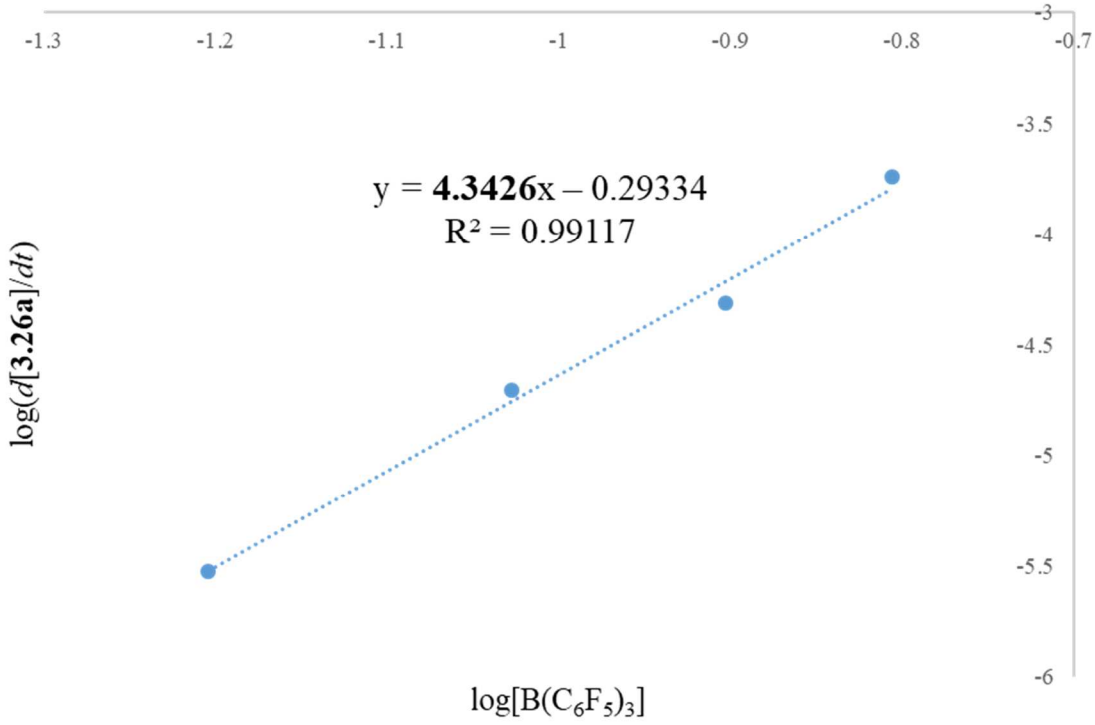
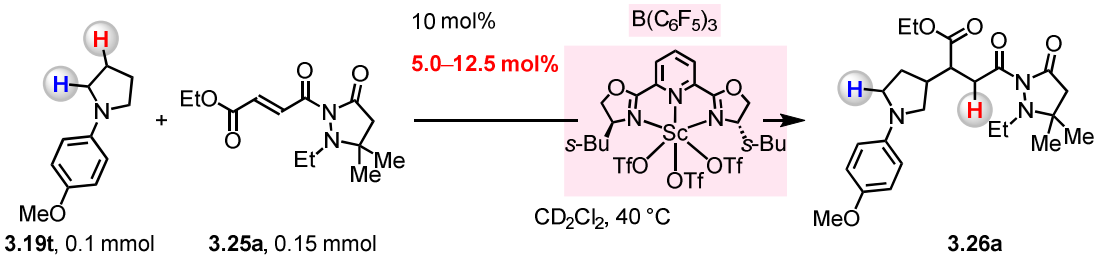


Figure S40. Log(rate) *vs* log[$B(C_6F_5)_3$] is employed to determine the initial reaction order for $B(C_6F_5)_3$. The result suggests that there is *fourth-order dependency* on $B(C_6F_5)_3$ concentration.

3.6.6.4.1.2. Reaction Order of L12–Sc(OTf)$_3$

The reaction between **3.19t** and **3.25a** was performed using different concentrations of **L12**–Sc(OTf)$_3$ and the progress of each reaction was monitored by the ^{1}H NMR spectroscopy (Scheme S25).

Scheme S25. Determination of the Reaction Order of **L12**–Sc(OTf)$_3$



In a nitrogen-filled glove box, B(C_6F_5)$_3$ (30.7 mg, 10 mol%), **3.19t** (106.2 mg, 0.6 mmol), **3.25a** (241.2 mg, 1.5 equiv) and toluene (55.2 mg, 1.0 equiv) were weighed in an oven-dried 7.0 mL vial and the resulting mixture was dissolved in 2.40 mL of CD_2Cl_2 (**Stock Solution A**). In another oven-dried 7.0 mL vial, **L12**–Sc(OTf)$_3$ (57.4 mg, 0.070 mmol) was weighed and dissolved in 1.40 mL of CD_2Cl_2 (**Stock Solution B**). To each J-Young tube was added **Stock Solution A** (0.40 mL), **Stock Solution B** (0.10, 0.15, 0.20, or 0.25 mL) and CD_2Cl_2 (0.30, 0.25, 0.20, or 0.15 mL) to prepare the reaction samples containing different concentrations of **L12**–Sc(OTf)$_3$. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and ^{1}H NMR spectra were acquired in the NMR spectrometer preheated at 40 °C using a pre-acquisition delay in array mode with a spectrum taken every 22 seconds for the length of the experiment. The data were processed using MestReNova software and peak integrations were normalized using toluene as the internal standard.

Initial-rate kinetic analysis, which was determined based on the data points acquired in the first 1100 seconds, showed that there is *–1-order dependency* on **L12**–Sc(OTf)$_3$ concentration in the

reaction between **3.19t** and **3.25a** (Figures S41, S42).

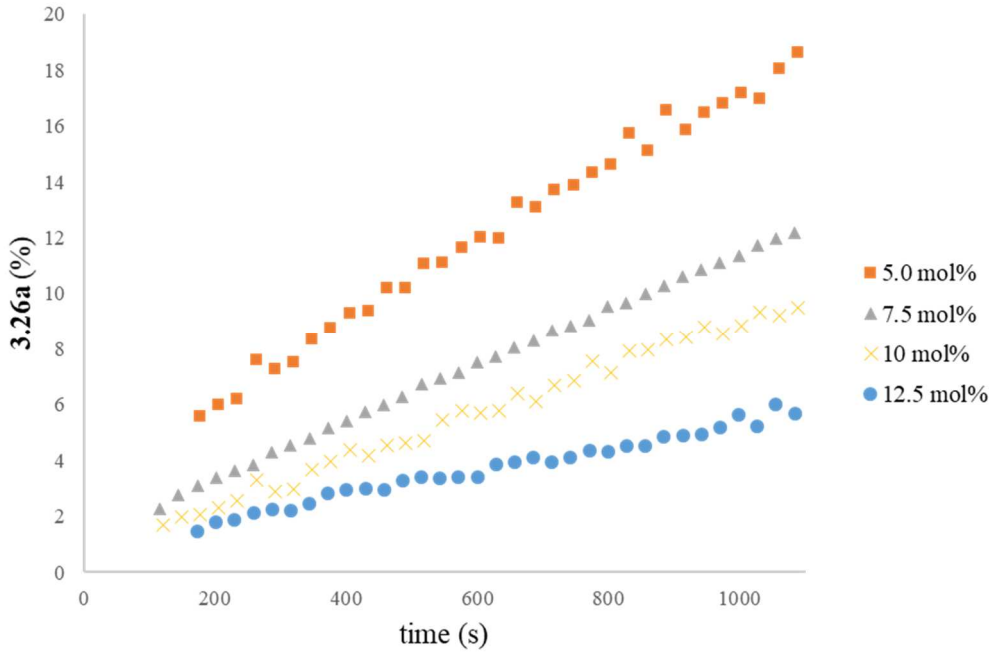


Figure S41. Monitoring the formation of **3.26a** under different concentrations of **L12**–$Sc(OTf)_3$

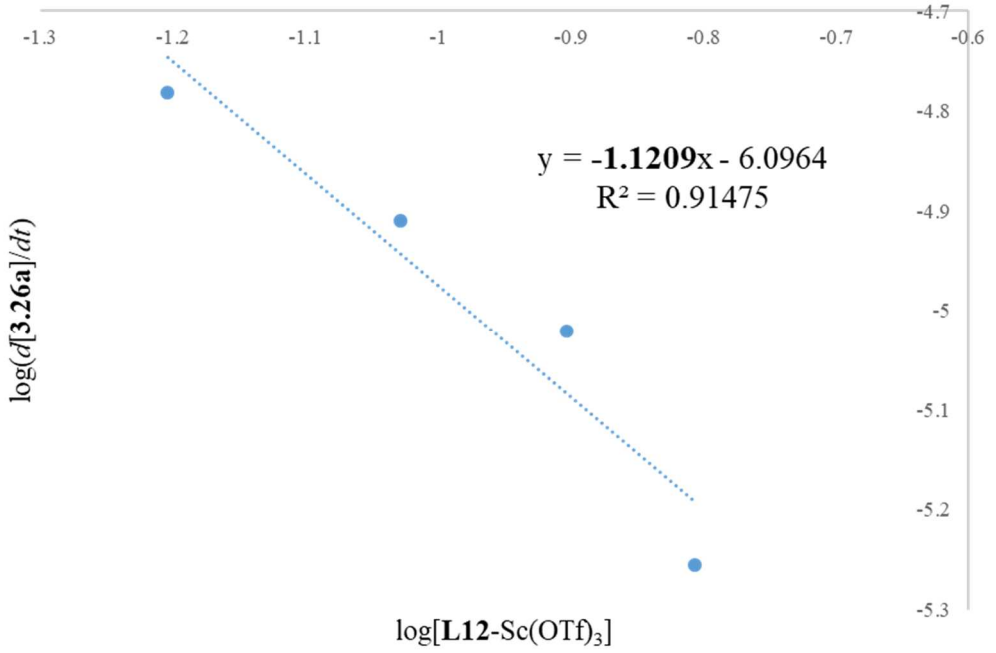
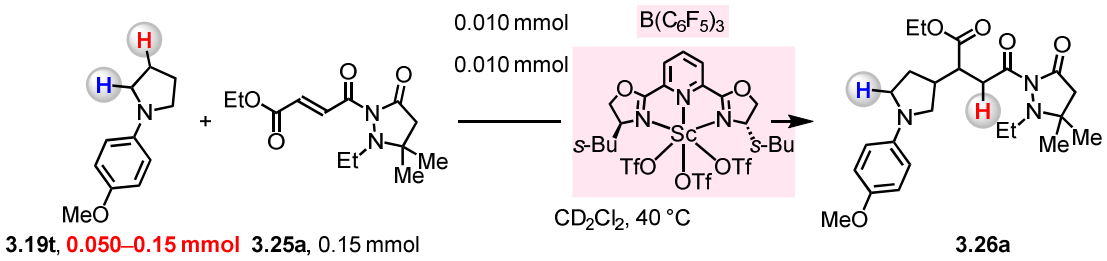


Figure S42. Log(rate) *vs* log[**L12**–$Sc(OTf)_3$] is employed to determine the initial reaction order for **L12**–$Sc(OTf)_3$. The result suggests that there is *–1-order dependency* on **L12**–$Sc(OTf)_3$ concentration.

3.6.6.4.1.3. Reaction Order of Amine

The reaction between **3.19t** and **3.25a** was performed using different concentrations of **3.19t** and the progress of each reaction was monitored by the ^{1}H NMR spectroscopy (Scheme S26).

Scheme S26. Determination of the Reaction Order of **3.19t**



In a nitrogen-filled glove box, $B(C_6F_5)_3$ (30.7 mg, 0.060 mmol), **L12**–$Sc(OTf)_3$ (24.6 mg, 0.030 mmol), **3.25a** (241.2 mg, 0.90 mmol) and toluene (55.2 mg, 0.60 mmol) were weighed in an oven-dried 7.0 mL vial and the resulting mixture was dissolved in 3.00 mL of CD_2Cl_2 (**Stock Solution A**). In another oven-dried 7.0 mL vial, **3.19t** (177mg, 1.0 mmol) was weighed and dissolved in 1.00 mL of CD_2Cl_2 (**Stock Solution B**). To each J-Young tube was added **Stock Solution A** (0.50 mL), **Stock Solution B** (0.05, 0.07, 0.10, or 0.15 mL) and CD_2Cl_2 (0.25, 0.23, 0.20, or 0.15 mL) to prepare the reaction samples containing different concentrations of **3.19t**. The reaction mixture was then transferred to a J-Young tube. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and ^{1}H NMR spectra were acquired in the NMR spectrometer preheated at 40 °C using a pre-acquisition delay in array mode with a spectrum taken every 22 seconds for the length of the experiment. The data were processed using MestReNova software and peak integrations were normalized using toluene as the internal standard.

Initial-rate kinetic analysis, which was determined based on the data points acquired in the first 800 seconds, showed that there is *first-order dependency* on amine **3.19t** concentration in the reaction between **3.19t** and **3.25a** (Figures S43, S44).

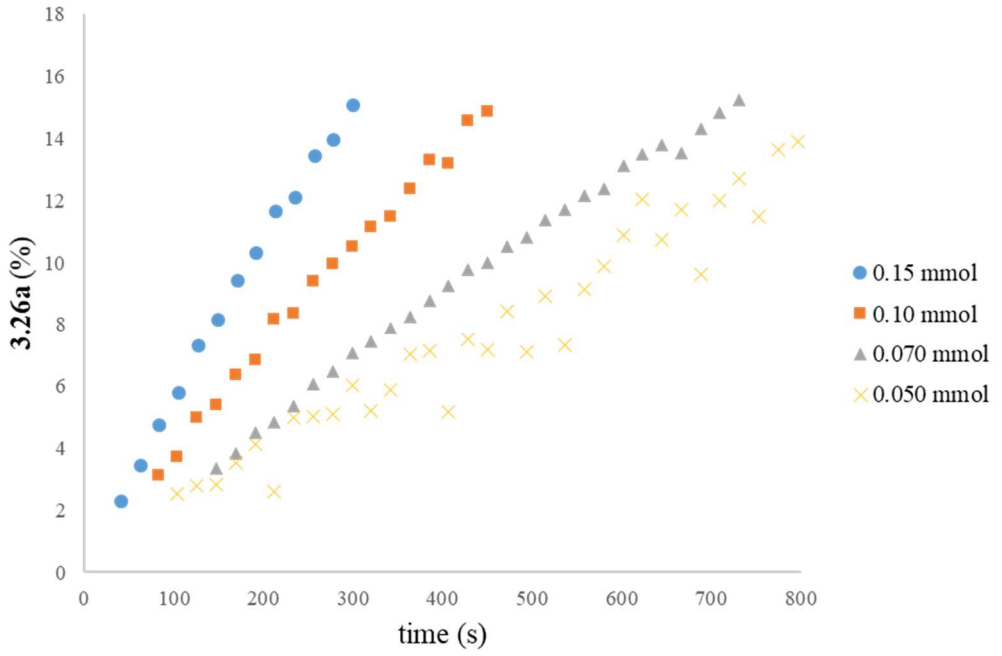


Figure S43. Monitoring the formation of **3.26a** under different concentrations of amine **3.19t**

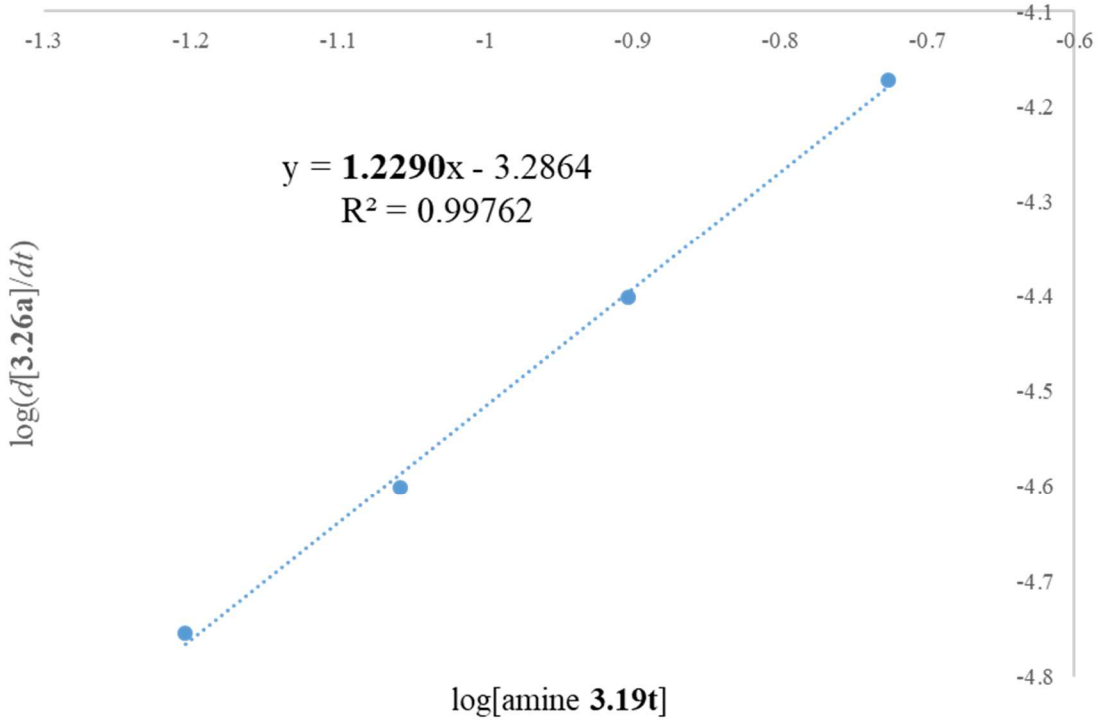
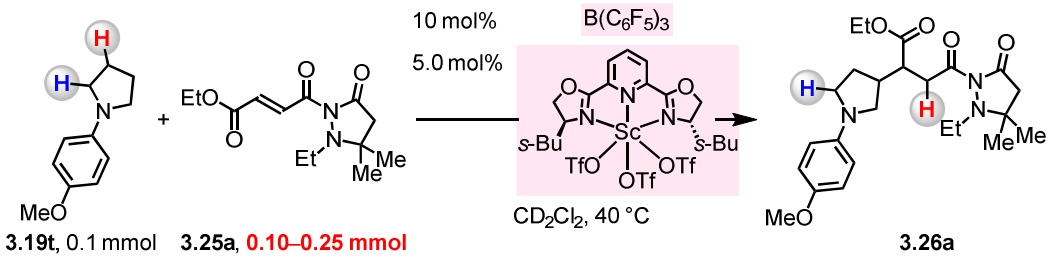


Figure S44. Log(rate) *vs* log[amine **3.19t**] is employed to determine the initial reaction order for amine **3.19t.** The result suggests that there is *first-order dependency* on **3.19t** concentration.

3.6.6.4.1.4 Reaction Order of α,β-Unsaturated Compound

The reaction between **3.19t** and **3.25a** was performed using different concentrations of **3.25a** and the progress of each reaction was monitored by the ^{1}H NMR spectroscopy (Scheme S27).

Scheme S27. Determination of the Reaction Order of **3.25a**



In a nitrogen-filled glove box, $B(C_6F_5)_3$ (30.7 mg, 10 mol%), **L12**–$Sc(OTf)_3$ (24.6 mg, 5.0 mol%), **3.19t** (106.2 mg, 0.60 mmol), and toluene (55.2 mg, 1.0 equiv) were weighed in an oven-dried 7.0 mL vial and the resulting mixture was dissolved in 3.00 mL of CD_2Cl_2 (**Stock Solution A**). In another oven-dried 7.0 mL vial, **3.25a** (322mg, 1.20 mmol) was weighed and dissolved in 1.20 mL of CD_2Cl_2 (**Stock Solution B**). To each J-Young tube was added **Stock Solution A** (0.50 mL), **Stock Solution B** (0.10, 0.15, 0.20, or 0.25 mL) and CD_2Cl_2 (0.20, 0.15, 0.10, or 0.05 mL) to prepare the reaction samples containing different concentrations of **3.25a**. The reaction mixture was then transferred to a J-Young tube. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and ^{1}H NMR spectra were acquired in the NMR spectrometer preheated at 40 °C using a pre-acquisition delay in array mode with a spectrum taken every 22 seconds for the length of the experiment. The data were processed using MestReNova software and peak integrations were normalized using toluene as the internal standard.

Initial-rate kinetic analysis, which was determined based on the data points acquired in the first 800 seconds, showed that there is *–3-order dependency* on α,β-unsaturated compound **3.25a** concentration in the reaction between **3.19t** and **3.25a** (Figures S45, S46).

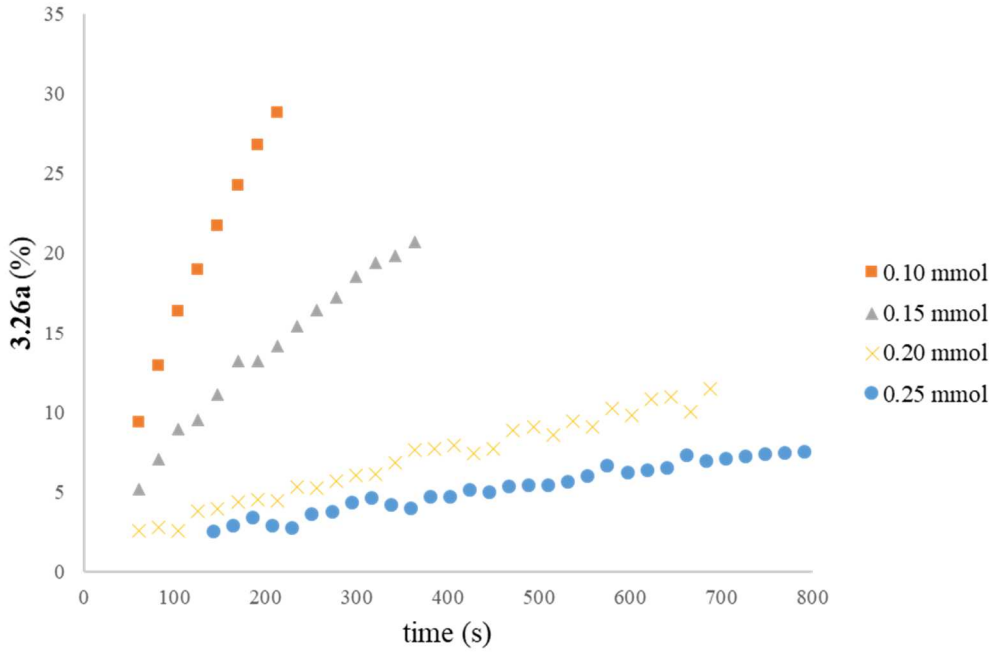


Figure S45. Monitoring the formation of **3.26a** under different concentrations of **3.25a**

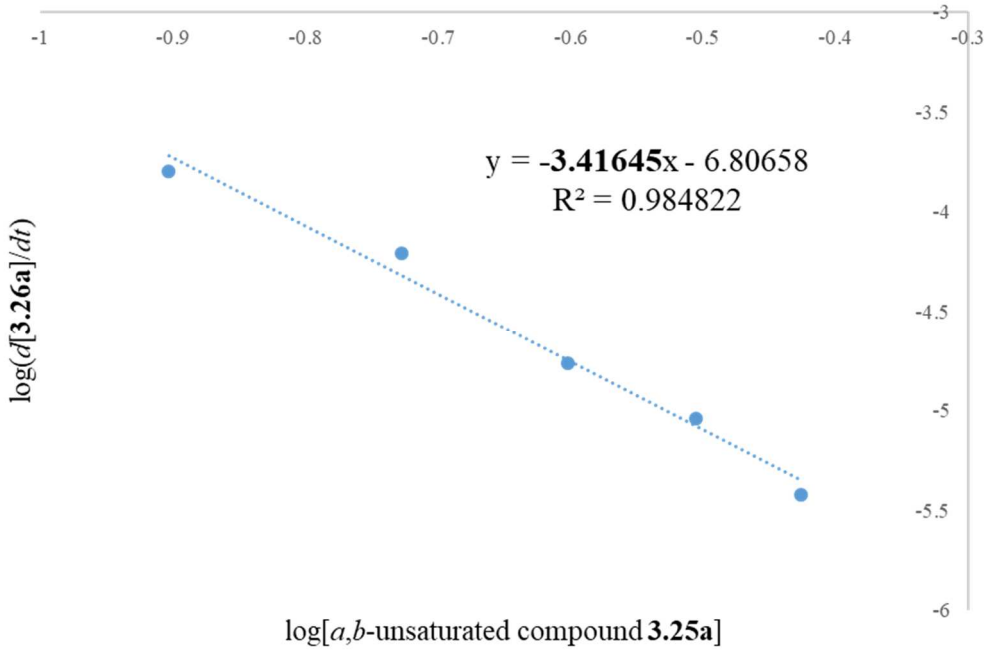


Figure S46. Log(rate) *vs* log[α,β-unsaturated compound **3.25a**] is employed to determine the initial reaction order for **3.25a**. The result suggests that there is *–3-order dependency* on **3.25a** concentration.

3.6.6.4.2. Kinetic Isotope Effect Experiments Involving 3.25a

In order to probe whether the turnover-limiting step involves the cleavage of α- or β-amino C–H bonds, we carried out parallel kinetic isotope effect experiments.

3.6.6.4.2.1. Parallel KIE Measurement for α-Amino C–H and C–D Bond Cleavage

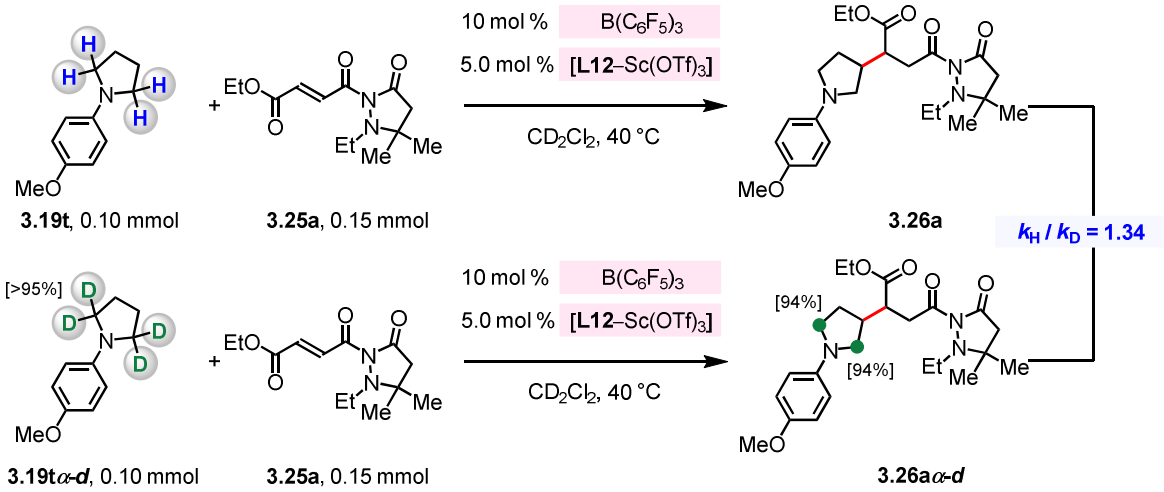
A parallel kinetic isotope effect study was conducted through time course reaction monitoring by the ^{1}H NMR spectroscopy using internal standard to monitor the difference in initial rates of the product formation in the reaction of 1-(4-methoxyphenyl)pyrrolidine **3.19t** or 1-(4-methoxyphenyl)pyrrolidine-2,2,5,5-d_4 **3.19t*α-d*** with ethyl (*E*)-4-(2-ethyl-3,3-dimethyl-5-oxopyrazolidin-1-yl)-4-oxobut-2-enoate **3.25a** (Scheme S28).

In a nitrogen-filled glove box, $B(C_6F_5)_3$ (20.4 mg, 0.040 mmol), **L12**–$Sc(OTf)_3$ (16.4 mg, 0.020 mmol), **3.25a** (160.8 mg, 0.60 mmol) and toluene (36.8 mg, 0.40 mmol) were weighed in an oven-dried 7.0 mL vial and the resulting mixture was dissolved in 2.00 mL of CD_2Cl_2 (**Stock Solution A**). In two oven-dried 7.0 mL vials were added **3.19t** (17.7 mg) or **3.19t*α-d*** (18.1 mg). To each oven-dried vial containing **3.19t** or **3.19t*α-d*** was added CD_2Cl_2 (0.30 mL) and **Stock Solution A** (0.50 mL) to prepare the reaction samples containing **3.19t** or **3.19t*α-d***. The reaction mixture was then transferred to a J-Young tube. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and ^{1}H NMR spectra were acquired in the NMR spectrometer preheated at 40 °C using a pre-acquisition delay in array mode with a spectrum taken every 22 seconds for the length of the experiment. The data were processed using MestReNova software and peak integrations were normalized using toluene as the internal standard.

Kinetic analysis based on the initial rates of the product formation (Figure S47) demonstrates that **3.19t** reacts 1.3 times faster than **3.19t*α-d*** (k_H/k_D = 1.34) in the reaction between **3.19t** or **3.19t*α-d*** and **3.25a**. From ^{1}H NMR analysis of the isolated and purified **3.26a*α-d*** in $CDCl_3$, it was

revealed that 94% of *d*-incorporation level was retained at the α-amino position (Figures S48−49). This result suggests that the borohydride reduction step may be irreversible as there was no H incorporation into the α-amino C−D bonds.

Scheme S28. Kinetic Isotope Effect Studies



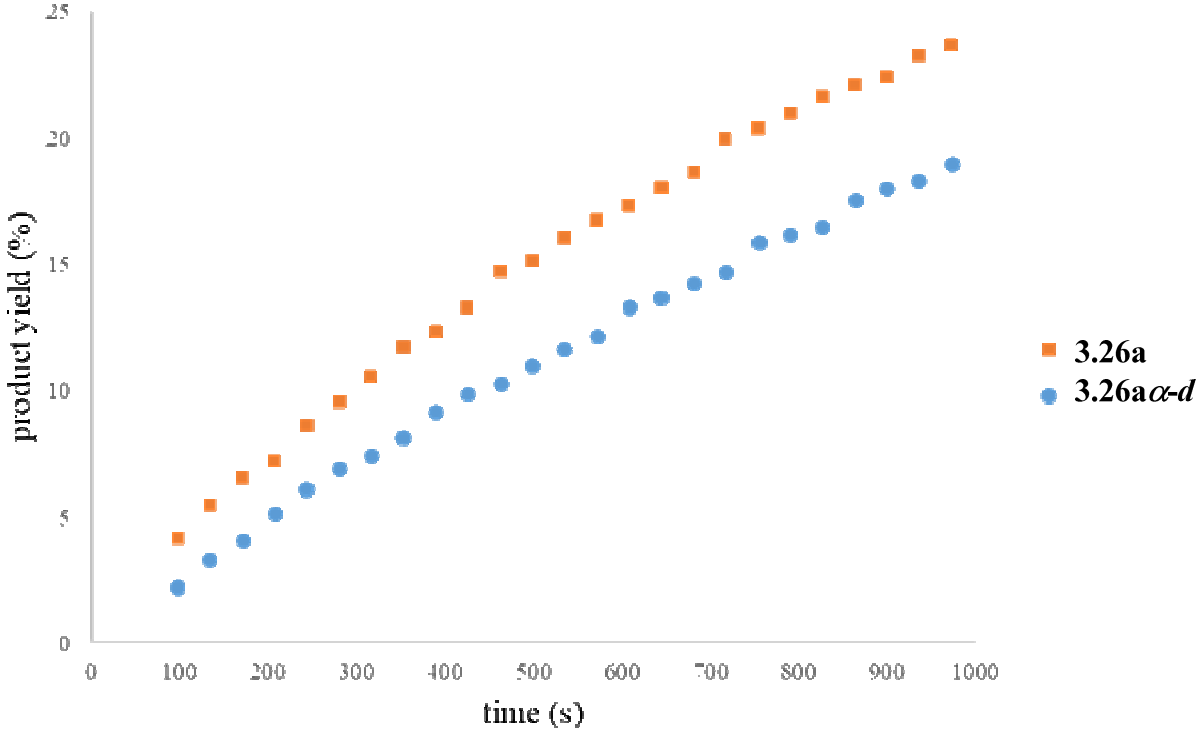


Figure S47. Monitoring the formation of products in parallel KIE measurements

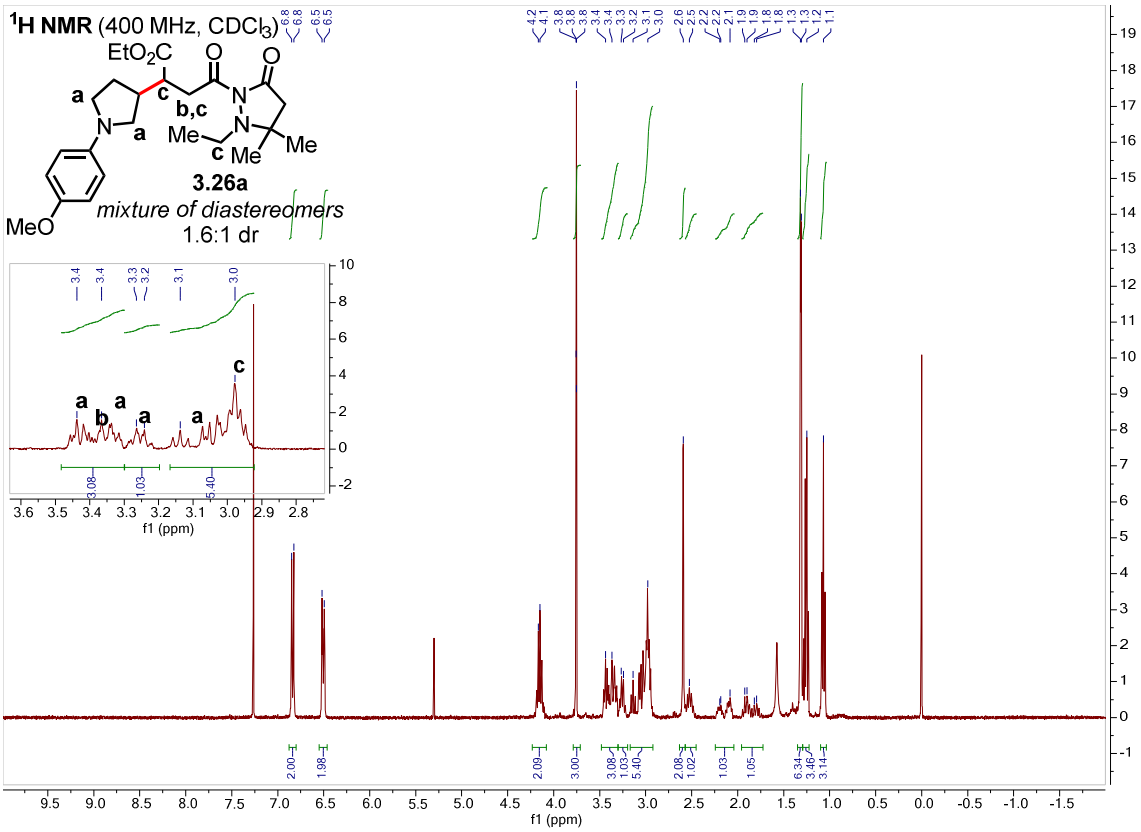


Figure S48. ^{1}H NMR spectrum of **3.26a** ($CDCl_3$)

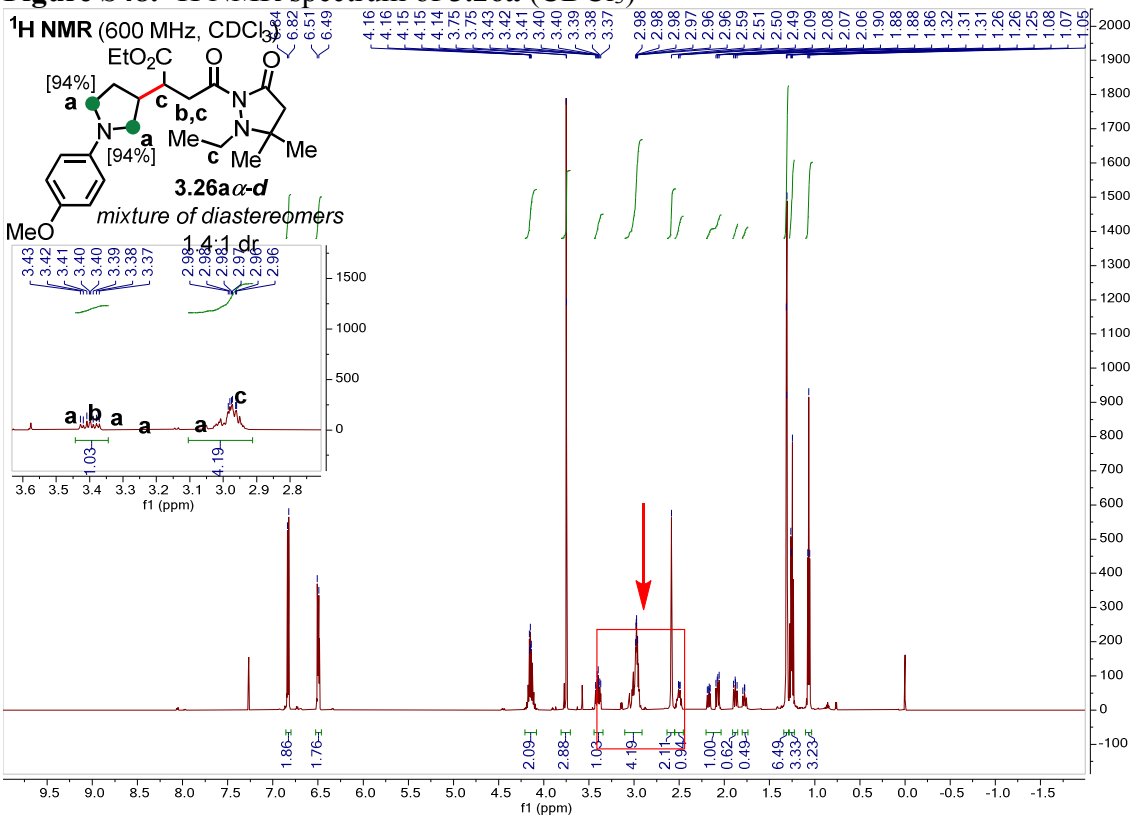


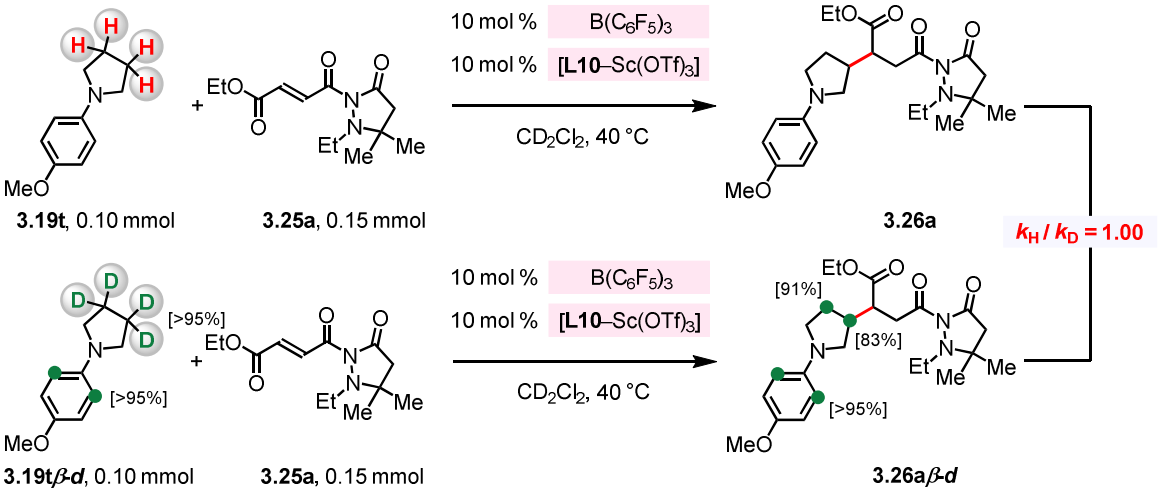
Figure S49. ^{1}H NMR spectrum of **3.26a*α-d*** ($CDCl_3$)

3.6.6.4.2.2. Parallel KIE Measurement for *β*-Amino C–H and C–D Bond Cleavage

A parallel kinetic isotope effect study was conducted through time course reaction monitoring by the ^{1}H NMR spectroscopy using internal standard to monitor the difference in initial rates of the product formation in the reaction of 1-(4-methoxyphenyl)pyrrolidine **3.19t** or 1-(4-methoxyphenyl)pyrrolidine-3,3,4,4-d_4 **3.19t*β-d*** with ethyl (*E*)-4-(2-ethyl-3,3-dimethyl-5-oxopyrazolidin-1-yl)-4-oxobut-2-enoate **3.25a** (Scheme S29). In a nitrogen-filled glove box, $B(C_6F_5)_3$ (20.4 mg, 0.040 mmol), **L12**–$Sc(OTf)_3$ (16.4 mg, 0.020 mmol), **3.25a** (160.8 mg, 0.60 mmol) and toluene (36.8 mg, 0.40 mmol) were weighed in an oven-dried 7.0 mL vial and the resulting mixture was dissolved in 2.00 mL of CD_2Cl_2 (**Stock Solution A**). In two oven-dried 7.0 mL vials were added **3.19t** (17.7 mg) or **3.19t*β-d*** (18.1 mg). To each oven-dried vial containing **3.19t** or **3.19t*β-d*** was added CD_2Cl_2 (0.30 mL) and **Stock Solution A** (0.50 mL) to prepare the reaction samples containing **3.19t** or **3.19t*β-d***. The reaction mixture was then transferred to a J-Young tube. After the J-Young tube was tightly capped with the Teflon plug, it was taken out of the glove box and ^{1}H NMR spectra were acquired in the NMR spectrometer preheated at 40 °C using a pre-acquisition delay in array mode with a spectrum taken every 22 seconds for the length of the experiment. The data were processed using MestReNova software and peak integrations were normalized using toluene as the internal standard.

Kinetic analysis based on the initial rates of the product formation (Figure S50) demonstrates no kinetic isotope effect (k_H/k_D = 1.00) in the reaction between **3.19t** or **3.19t*β-d*** and **3.25a**. From ^{1}H NMR analysis of the isolated and purified **3.26a*β-d*** in $CDCl_3$ and acetone-d_6, *d*-incorporation level was determined (Figures S51–54).

Scheme S29. Kinetic Isotope Effect Studies



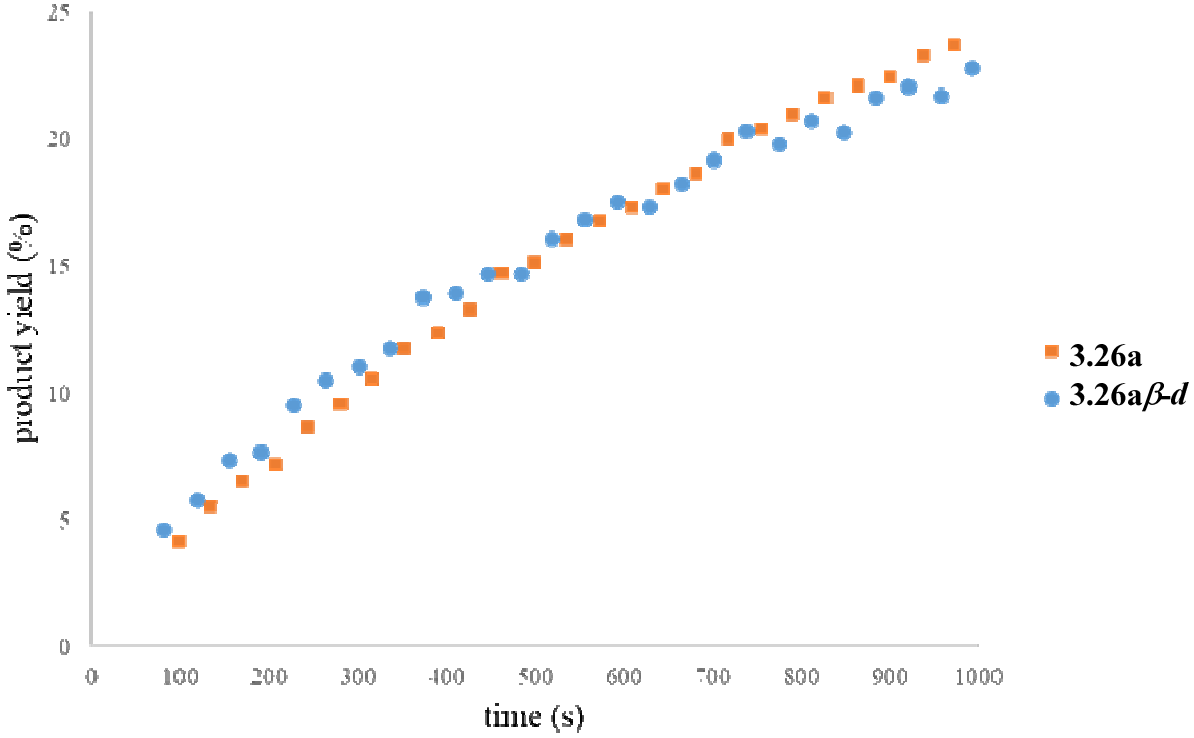


Figure S50. Monitoring the formation of products in parallel KIE measurements

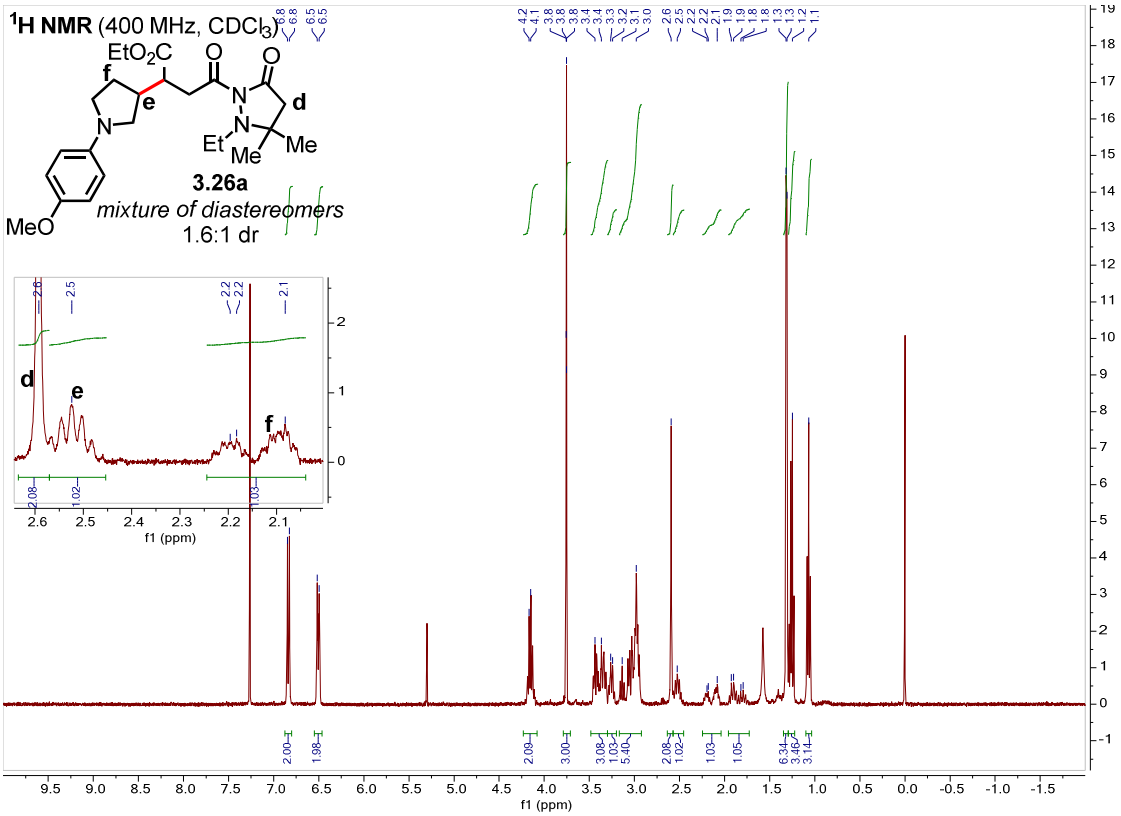


Figure S51. ^{1}H NMR spectrum of **3.26a** ($CDCl_3$)

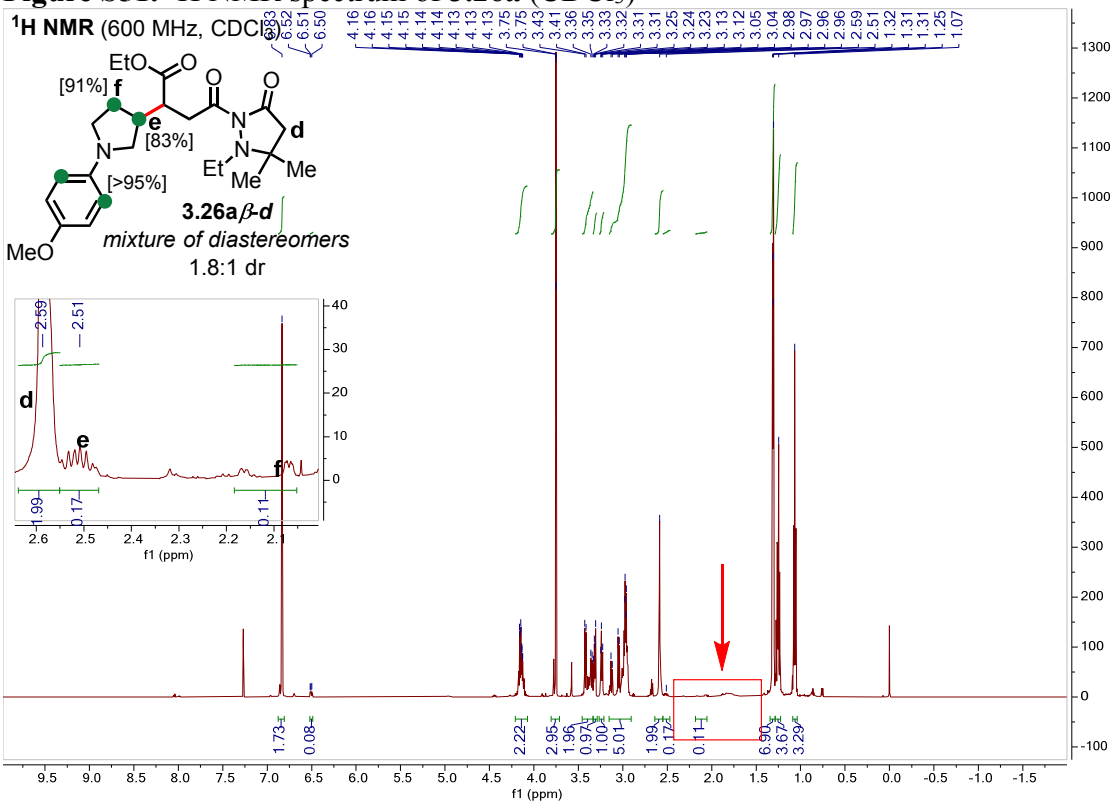


Figure S52. ^{1}H NMR spectrum of **3.26a*β-d*** ($CDCl_3$)

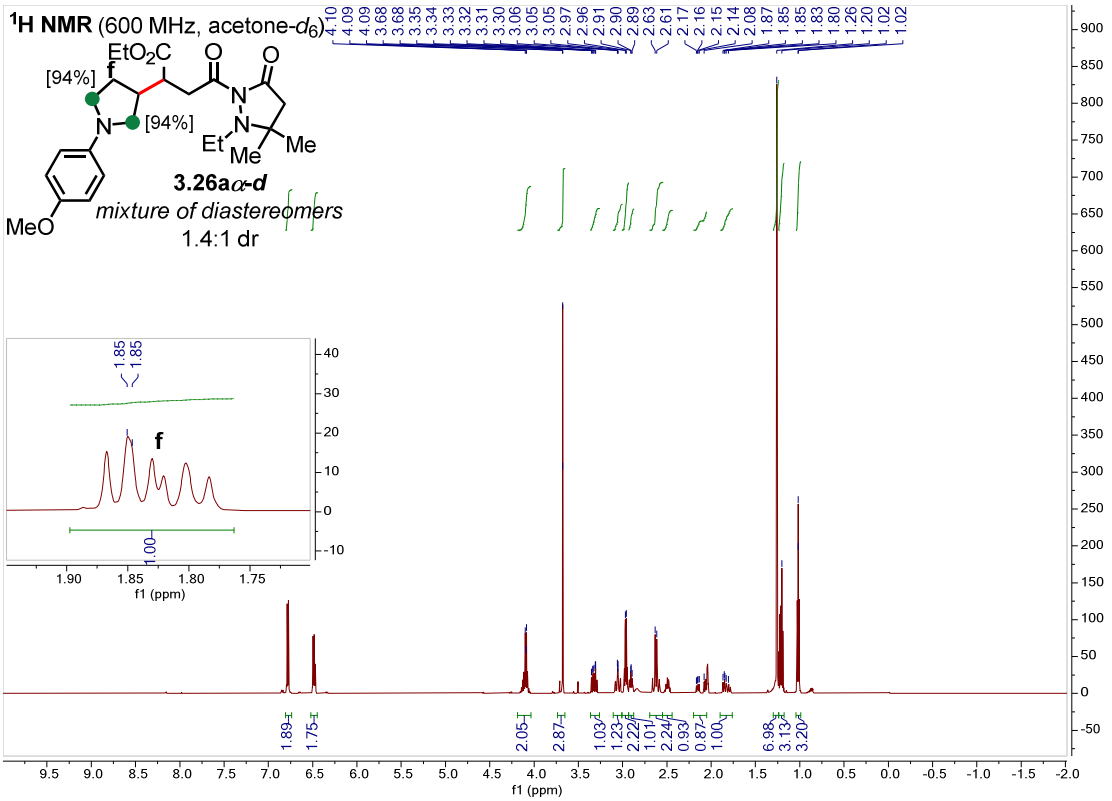


Figure S53. ^{1}H NMR spectrum of **3.26a*α*-*d*** (acetone-d_6)

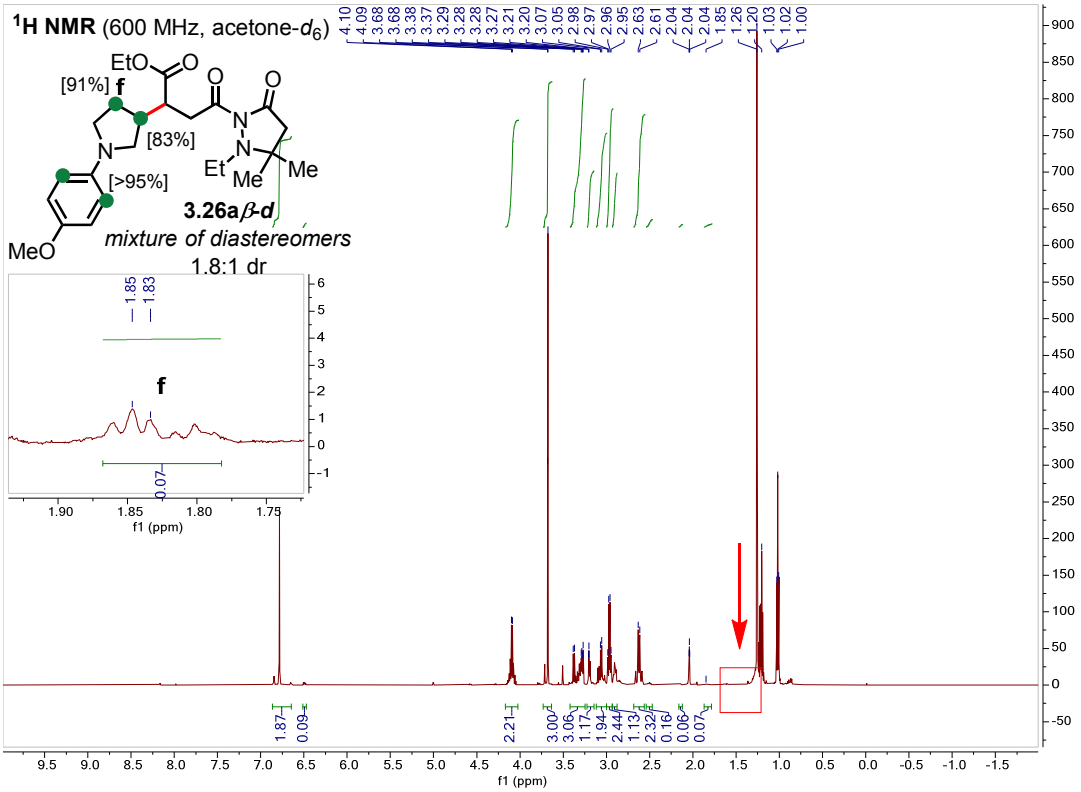


Figure S54. ^{1}H NMR spectrum of **3.26a*β*-*d*** (acetone-d_6)

3.6.6.4.3. The ^{13}C NMR Experiments for Characterization of Resting State Complexes

The mechanistic investigation revealed that the $(F_5C_6)_3B$/**L12**–$Sc(OTf)_3$ co-catalyzed *β*-amino C–H functionalization has a *–1 order dependency* with respect to the concentration of **L12**–$Sc(OTf)_3$ (see **Section 3.6.6.4.1.2**) and *–3 order dependency* with respect to the concentration of ethyl (*E*)-4-(2-ethyl-3,3-dimethyl-5-oxopyrazolidin-1-yl)-4-oxobut-2-enoate **3.25a** (see **Section 3.6.6.4.1.4**). We hypothesized that [**L12**–$Sc(OTf)_3$]–**3.25a**–$B(C_6F_5)_3$ adduct could be the resting state and carried out the ^{13}C NMR experiments to identify the structure of the resting state complex (Figures S55, S56). Previously, the group of Piers has reported that $B(C_6F_5)_3$ and benzaldehyde forms $(F_5C_6)_3B$–carbonyl compound adduct which showed that ^{13}C NMR peak of carbonyl moiety shifted further downfield to 199.4 ppm. We acquired the ^{13}C NMR spectra of a sample containing $B(C_6F_5)_3$ and/or **L12**–$Sc(OTf)_3$ and **3.25a** in CD_2Cl_2 (Figures S55, S56).

In the ^{13}C NMR spectrum of a reaction mixture containing **3.25a** and 50 mol% $B(C_6F_5)_3$, it was observed that the carbonyl peak of **3.25a** at 175.3 ppm has shifted to 178.1 ppm (Figure S55A, S51B. See the peak marked with a red arrow). Similar trend was observed in a mixture of **3.25a**, 50 mol% $B(C_6F_5)_3$, and 25 mol% **L12**–$Sc(OTf)_3$ showing shifted peak at 178.4 ppm (Figure S55C, S56). Furthermore, the peak at 162.5 ppm of **3.25a** shifted to 163.5 ppm, which was also detected in the solution of **3.25a** and 25 mol% **L12**–$Sc(OTf)_3$ (Figure S55C, S55D, and S56. See the peak marked with a blue arrow).

These results are in agreement with our hypothesis that Lewis acidic $B(C_6F_5)_3$ and **L12**–$Sc(OTf)_3$ coordinate to Lewis basic carbonyl functional groups of **3.25a** and form [**L12**–$Sc(OTf)_3$]–**3.25a**–$B(C_6F_5)_3$ adduct as the catalyst resting state.

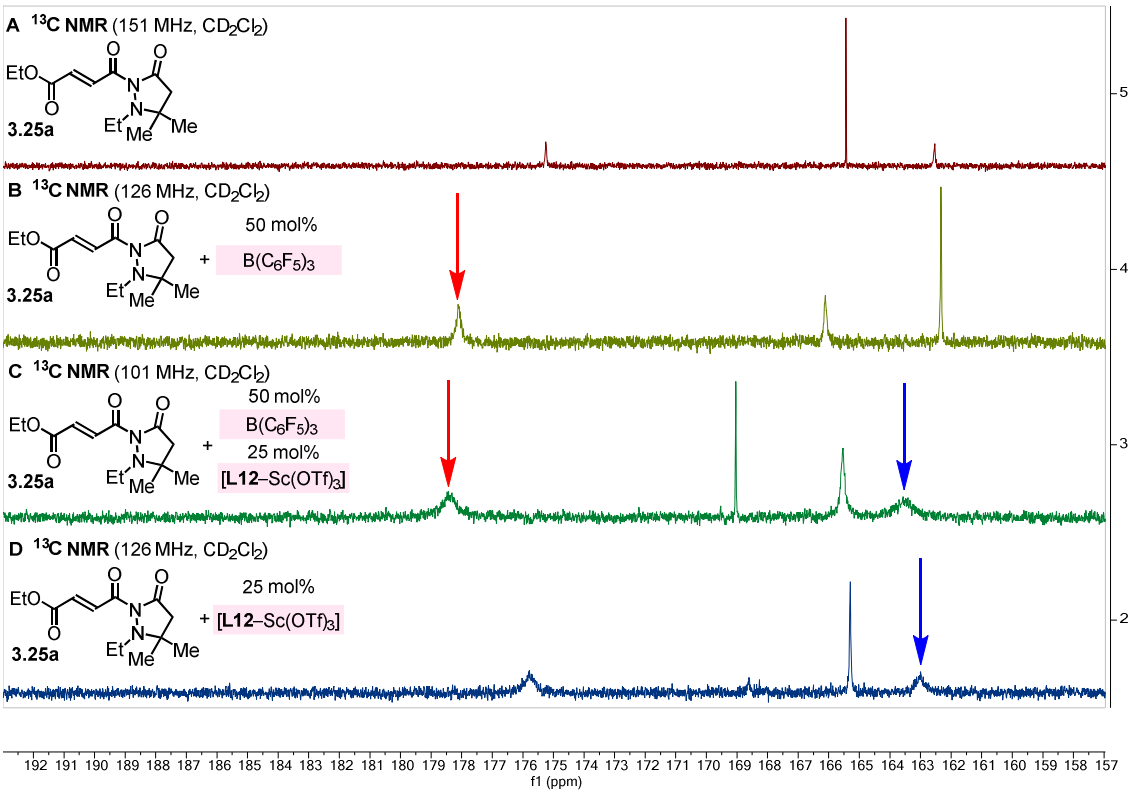


Figure S55. ^{13}C NMR experiments for the detection of the resting state

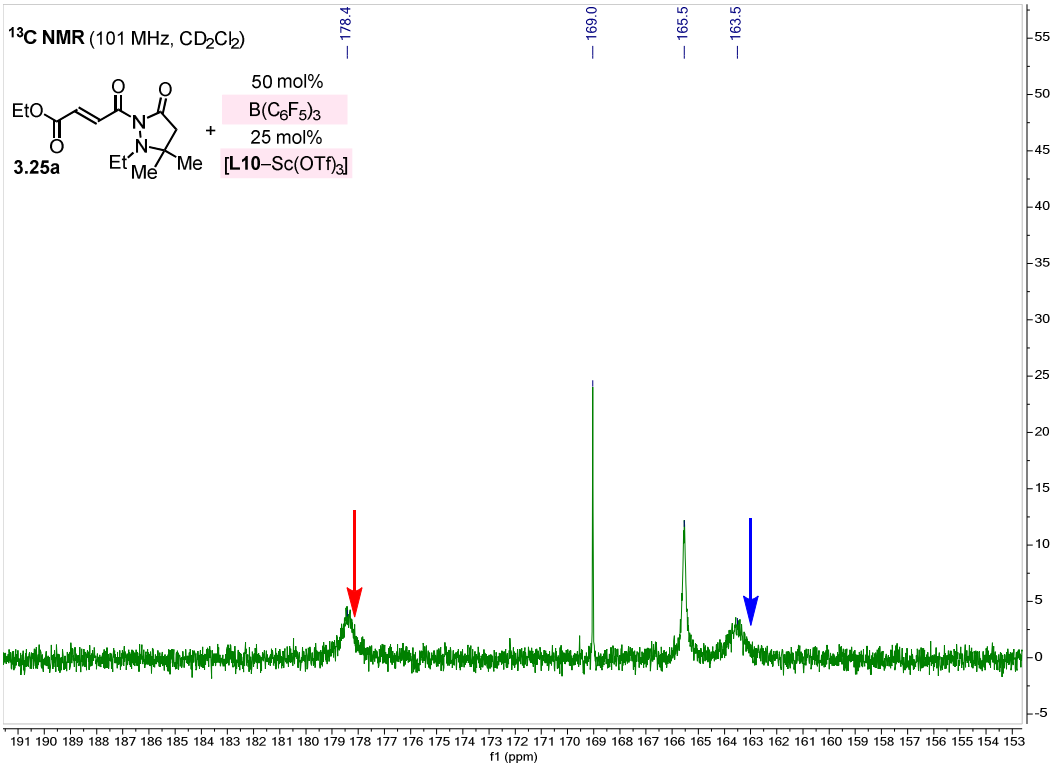


Figure S56. ^{13}C NMR spectrum of 3.25a, B(C_6F_5)$_3$, and L12–Sc(OTf)$_3$

3.6.6.5. Catalytic Cycle for the Enantioselective β-Amino C–H Functionalization Involving 3.25a

In Figure S57, we show the catalytic cycles that are consistent with the above-mentioned mechanistic investigations (**Section 3.6.6.4**). The studies discussed in **Section 3.6.6.4.3** revealed that there is *–1 order dependency* with respect to the concentration of **L12**–$Sc(OTf)_3$ (**Section 3.6.6.4.1.2**) and *–3 order dependency* with respect to the concentration of **3.25** (**Section 3.6.6.4.1.4**). These results suggest that there is a resting state complex comprised of [**L12**–$Sc(OTf)_3$], **3.25a**, and $B(C_6F_5)_3$ (**XXIX**) which was verified by the ^{13}C NMR studies (Figures S55, S56). $B(C_6F_5)_3$ released from **XXIX** abstracts a hydride from **3.19t** to form an ion pair consisting of iminium ion and borohydride (**XXX**). The *fourth order dependency* with respect to the concentration of $B(C_6F_5)_3$ (**Section 3.6.6.4.1.1**) and the kinetic isotope effect studies (**Section 3.6.6.4.2**) suggest that the borohydride reduction of $(F_5C_6)_3B$-activated **3.25a** is the turnover-limiting step (**XXX** → **XXXI**). After the protonation of enolate (**XXXI** → **XXXII**), nucleophilic enamine can undergo enantioselective C–C bond formation with [**L12**–$Sc(OTf)_3$]-activated **3.25a** to form zwitterionic **XXXIV**. As discussed in **Section 3.6.6.3**, we propose that **3.19t** could serve as H^+/H^- source to reduce **XXXIV** in order to afford the desired β-alkylation product **3.26a**.

The results from the mechanistic investigations involving **3.25a** (**Section 3.6.6.4**) are in similar trend with the proposed catalytic cycle that was based on the mechanistic studies involving aryl-substituted electrophile **3.25e** (Figure S35, **Section 3.6.6.1–3.6.6.2**). However, it was found that the turnover-limiting step could be different depending on the electrophile that is used. When ethyl ester-substituted electrophile **3.25a** is involved, the borohydride reduction step (turnover-limiting) becomes irreversible as the allylic C–H bond of the boron–enolate (blue H in **XXXI**, Figure S57)

is not as hydridic due to the electron withdrawing ester unit (vs phenyl substituent in **3.25e**).

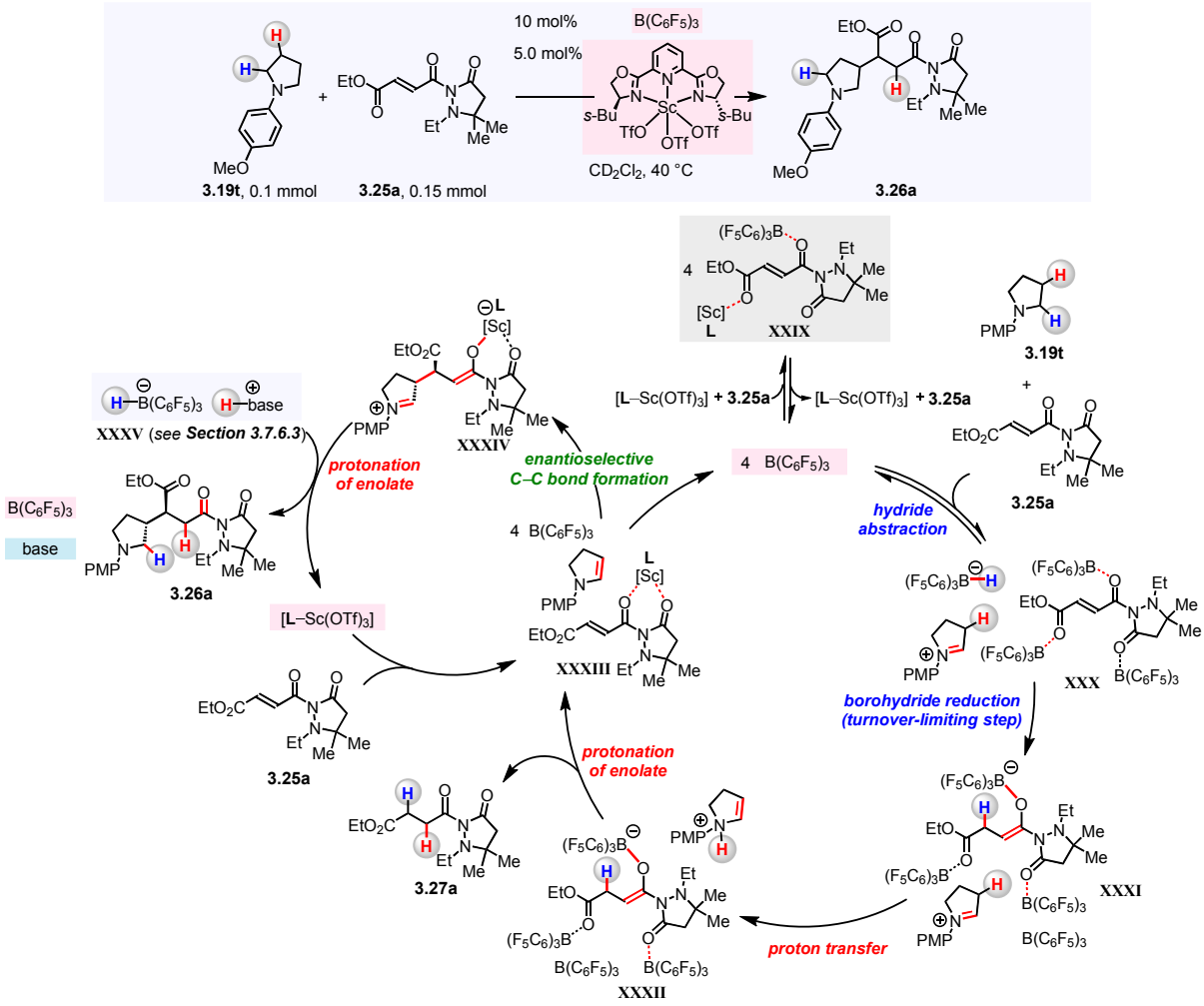
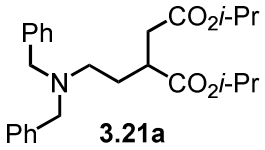


Figure S57. Proposed catalytic cycle for the enantioselective *β*-amino C–H functionalization involving **3.25a**

3.6.7. Analytical Data

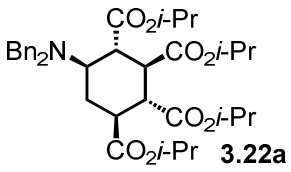


3.21a

Diisopropyl 2-(2-(dibenzylamino)ethyl)succinate (3.21a)

N,*N*-Dibenzylethanamine **3.19a** was reacted with diisopropyl fumarate **3.20a** following the **General Procedure C** using $B(C_6F_5)_3$ (10 mol%) as the Lewis acid catalyst and benzene (0.80 mL) as the solvent. After purification by column chromatography (ethyl ether:hexanes = 1:19), **3.21a** was obtained as a colorless liquid (75 mg, 88%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 (d, *J* = 7.5 Hz, 4H), 7.29 (t, *J* = 7.5 Hz, 4H), 7.22 (t, *J* = 7.3 Hz, 2H), 4.95 (dp, *J* = 26.6, 6.2 Hz, 2H), 3.61 (d, *J* = 13.6 Hz, 2H), 3.46 (d, *J* = 13.5 Hz, 2H), 2.88 (dq, *J* = 12.4, 6.6 Hz, 1H), 2.51 – 2.39 (m, 3H), 2.16 (dd, *J* = 16.4, 5.1 Hz, 1H), 1.92 (dq, *J* = 14.4, 7.3 Hz, 1H), 1.61 (h, *J* = 7.3 Hz, 1H), 1.20 (d, *J* = 6.3 Hz, 6H), 1.16 (d, *J* = 6.3 Hz, 3H), 1.12 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 174.3, 171.3, 139.5, 128.8, 128.2, 126.9, 67.78, 67.77, 58.3, 50.5, 39.1, 35.9, 29.0, 21.81, 21.78, 21.69, 21.65; **IR (neat):** ν 2976, 2932, 2796, 1724, 1452, 1372, 1260, 1168, 1104, 745, 698 cm^{-1}; **HRMS (ESI):** Calcd for $C_{26}H_{36}NO_4$ (MH^+): 426.2639; found: 426.2643.

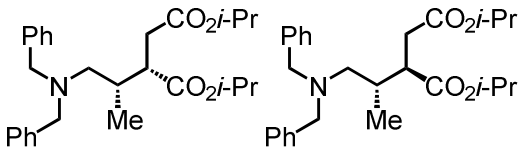


3.22a

Tetraisopropyl 5-(dibenzylamino)cyclohexane-1,2,3,4-tetracarboxylate (3.22a)

The relative configuration was assigned based on NOESY experiments (see **Section 3.6.3** for NOE spectrum).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.27 (m, 8H), 7.22 (t, *J* = 6.6 Hz, 2H), 5.06 (hept, *J* = 6.4 Hz, 1H), 5.02 – 4.89 (m, 3H), 3.89 (d, *J* = 13.6 Hz, 2H), 3.48 (d, *J* = 13.6 Hz, 2H), 3.38 (t, *J* = 8.3 Hz, 1H), 3.30 (t, *J* = 8.3 Hz, 1H), 2.81 – 2.66 (m, 3H), 2.57 (dd, *J* = 16.7, 10.1 Hz, 1H), 2.44 (dd, *J* = 16.8, 3.6 Hz, 1H), 1.31 (d, *J* = 6.3 Hz, 3H), 1.27 (d, *J* = 6.2 Hz, 3H), 1.21 (td, *J* = 6.0, 3.7 Hz, 12H), 1.16 (d, *J* = 6.2 Hz, 3H), 1.11 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 172.3, 172.2, 172.1, 171.1, 139.1, 128.9, 128.4, 127.3, 68.4, 68.3, 67.9, 60.8, 54.8, 45.3, 42.3, 41.2, 39.4, 34.2, 22.0, 21.91, 21.88, 21.87, 21.78, 21.76, 21.7; **IR (neat):** ν 2977, 2934, 1725, 1493, 1373, 1258, 1201, 1175, 1106, 748, 699 cm^{-1}; **HRMS (DART):** Calcd for $C_{36}H_{50}NO_8$ (MH^+): 624.3531; found: 624.3511.



3.21b-major **3.21b-minor**

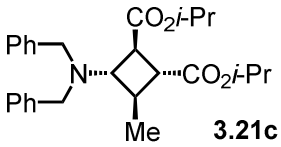
Diisopropyl 2-(1-(dibenzylamino)propan-2-yl)succinate (3.21b)

N,N-Dibenzylpropan-1-amine **3.19b** was reacted with diisopropyl fumarate **3.20a** following the **General Procedure C** using $B(C_6F_5)_3$ (10 mol%) as the Lewis acid catalyst and benzene (0.2 mL) as the solvent. ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was 1.3:1. After purification by column chromatography (ethyl ether:hexanes = 1:19), **3.21b** was obtained as a mixture of diastereomers (51 mg, 58%). **3.21c** was obtained as a colorless liquid (29 mg, 33%). Further purification was carried out by PTLC using ethyl ether:DCM = 1:49 as the eluent to separate **3.21b-major** and **3.21b-minor**. The relative configuration of **3.21b-major** was assigned in analogy as described in **Section 3.6.3**.

3.21b-Major: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.1 Hz, 4H), 7.28 (t, *J* = 7.5 Hz, 4H), 7.21 (t, *J* = 7.3 Hz, 2H), 4.99 (h, *J* = 6.3 Hz, 2H), 3.75 (d, *J* = 13.3 Hz, 2H), 3.34 – 3.26 (m, 3H),

2.39 – 2.30 (m, 2H), 2.24 (dd, *J* = 12.8, 9.7 Hz, 1H), 2.14 (dd, *J* = 12.9, 6.0 Hz, 1H), 1.56 (dd, *J* = 16.7, 3.2 Hz, 1H), 1.27 – 1.19 (m, 9H), 1.16 (d, *J* = 6.2 Hz, 3H), 0.73 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.5, 172.0, 139.5, 129.1, 128.2, 126.9, 67.6, 67.5, 58.7, 56.8, 42.1, 32.1, 29.8, 21.9, 21.84, 21.83, 21.7, 13.9; **IR** (neat) ν 2976, 2930, 2799, 1723, 1452, 1372, 1232, 1172, 1105, 745, 698 cm^{-1}; **HRMS** (DART) Calcd for $C_{27}H_{38}NO_4$ (MH^+): 440.2795; found: 440.2789.

3.21b-Minor: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.5 Hz, 4H), 7.29 (t, *J* = 7.5 Hz, 4H), 7.22 (t, *J* = 7.2 Hz, 2H), 4.96 (dp, *J* = 22.6, 6.3 Hz, 1H), 3.71 (d, *J* = 13.6 Hz, 2H), 3.32 (d, *J* = 13.6 Hz, 2H), 2.91 (dt, *J* = 10.7, 4.1 Hz, 1H), 2.62 (dd, *J* = 16.6, 10.7 Hz, 1H), 2.41 (dd, *J* = 12.7, 5.8 Hz, 1H), 2.32 (dd, *J* = 12.7, 8.8 Hz, 1H), 2.15 (dd, *J* = 16.6, 4.3 Hz, 1H), 1.98 (ddp, *J* = 9.8, 6.4, 3.7, 3.1 Hz, 1H), 1.21 (dd, *J* = 11.4, 6.2 Hz, 6H), 1.16 (d, *J* = 6.3 Hz, 3H), 1.06 (d, *J* = 6.3 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.1, 171.8, 139.5, 128.9, 128.1, 126.8, 107.3, 67.8, 59.0, 58.7, 44.3, 34.2, 33.5, 21.82, 21.79, 21.76, 21.7, 15.2; **HRMS** (DART) Calcd for $C_{27}H_{38}NO_4$ (MH^+): 440.2795; found: 440.2780.

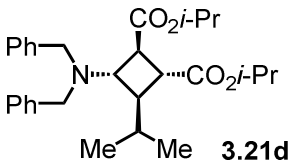


3.21c

Diisopropyl 3-(dibenzylamino)-4-methylcyclobutane-1,2-dicarboxylate (3c)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.6 Hz, 4H), 7.28 (t, *J* = 7.5 Hz, 4H), 7.21 (t, *J* = 7.3 Hz, 2H), 5.00 (dp, *J* = 16.7, 6.3 Hz, 2H), 3.79 (d, *J* = 14.0 Hz, 2H), 3.63 (d, *J* = 14.1 Hz, 2H), 3.30 (t, *J* = 8.7 Hz, 1H), 3.11 (t, *J* = 8.4 Hz, 1H), 2.51 – 2.36 (m, 2H), 1.27 (d, *J* = 6.2 Hz, 3H), 1.24 (d, *J* = 6.2 Hz, 3H), 1.21 (t, *J* = 6.1 Hz, 6H), 1.10 (d, *J* = 5.8 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$)

δ 172.7, 172.5, 139.6, 128.4, 128.2, 126.9, 67.91, 67.90, 64.2, 54.7, 43.0, 41.7, 37.3, 21.9, 21.81, 21.78, 21.76, 18.7; **IR** (neat) ν 2977, 2927, 1723, 1453, 1373, 1233, 1174, 1107, 746, 698 cm^{-1}; **HRMS** (DART) Calcd for $C_{27}H_{36}NO_4$ (MH^+): 438.2639; found: 438.2623.

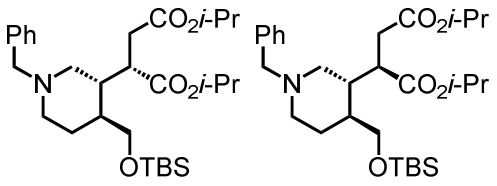


3.21d

Diisopropyl 3-(dibenzylamino)-4-isopropylcyclobutane-1,2-dicarboxylate (3.21d)

N,*N*-Dibenzyl-3-methylbutan-1-amine **3.19c** was reacted with diisopropyl fumarate **3.20a** following the **General Procedure D** using $B(C_6F_5)_3$ (10 mol%) as the Lewis acid catalyst and benzene as the solvent. ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was >20:1. After purification by column chromatography (ethyl ether:hexanes = 1:33), **3.21d** was obtained as a colorless liquid (64 mg, 69%). The relative configuration was assigned based on NOESY experiments.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, *J* = 6.8 Hz, 4H), 7.29 (t, *J* = 7.6 Hz, 4H), 7.22 (t, *J* = 7.2 Hz, 2H), 5.02 (dp, *J* = 32.2, 6.3 Hz, 2H), 3.92 (d, *J* = 13.6 Hz, 2H), 3.50 (d, *J* = 13.6 Hz, 2H), 3.34 (t, *J* = 8.6 Hz, 1H), 3.26 (t, *J* = 8.7 Hz, 1H), 2.55 (t, *J* = 8.8 Hz, 1H), 2.28 (q, *J* = 8.7 Hz, 1H), 1.56 – 1.49 (m, 1H), 1.31 (d, *J* = 6.3 Hz, 3H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.21 (dd, *J* = 9.3, 6.3 Hz, 6H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.78 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.4, 172.8, 139.6, 128.8, 128.2, 126.9, 68.0, 67.9, 60.9, 54.7, 48.5, 41.0, 39.1, 32.7, 21.9, 21.82, 21.80, 21.6, 20.2, 19.7; **IR** (neat) ν 2976, 2931, 1720, 1453, 1372, 1227, 1171, 1105, 747, 698 cm^{-1}; **HRMS** (DART) Calcd for $C_{29}H_{40}NO_4$ (MH^+): 466.2952; found: 466.2941.



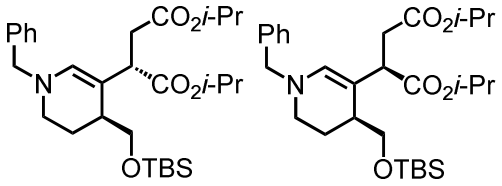
3.21e-major **3.21e-minor**

Diisopropyl 2-(1-benzyl-4-(((*tert*-butyldimethylsilyl)oxy)methyl)piperidin-3-yl)succinate (3.21e)

1-Benzyl-4-(((*tert*-butyldimethylsilyl)oxy)methyl)piperidine **3.19d** was reacted with diisopropyl fumarate **2.20a** following the **General Procedure C** using $B(C_6F_5)_3$ (10 mol%) as the Lewis acid catalyst and benzene (0.2 mL) as the solvent. ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was 1.1:1. After purification by column chromatography (ethyl ether:hexanes = 1:4), **3.21e** was obtained as a mixture of diastereomers (77.0 mg, 74%). Further purification was carried out by PTLC using ethyl ether:DCM = 1:6 as the eluent to separate **3.21e-major** and **3.21e-minor**. The relative configuration for **3.21e-major** and **3.21e-minor** were assigned based on X-ray crystallography data (see **Sections 3.6.3**).

3.21e-Major: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (dp, *J* = 22.0, 7.5 Hz, 5H), 4.98 (dp, *J* = 16.3, 6.4 Hz, 2H), 3.71 (dd, *J* = 10.0, 2.6 Hz, 1H), 3.65 (dd, *J* = 10.1, 5.1 Hz, 1H), 3.52 (d, *J* = 13.4 Hz, 1H), 3.41 (d, *J* = 13.4 Hz, 1H), 3.09 (dt, *J* = 11.2, 3.4 Hz, 1H), 2.82 (tt, *J* = 16.1, 10.8 Hz, 3H), 2.22 (dd, *J* = 16.7, 3.7 Hz, 1H), 1.85 (t, *J* = 11.2 Hz, 1H), 1.82 – 1.77 (m, 1H), 1.76 – 1.63 (m, 2H), 1.46 (pt, *J* = 11.9, 6.7 Hz, 2H), 1.21 (dt, *J* = 12.1, 6.0 Hz, 12H), 0.87 (d, *J* = 3.2 Hz, 9H), 0.03 (d, *J* = 2.9 Hz, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.7, 171.6, 138.2, 129.1, 129.0, 128.2, 128.1, 126.9, 67.91, 67.86, 64.6, 63.3, 55.4, 53.3, 40.7, 40.4, 40.0, 35.3, 29.3, 26.0, 25.9, 21.9, 21.82, 21.80, 21.75, 18.3, -5.4, -5.5; **IR** (neat) ν 2950, 2854, 1727, 1466, 1372, 1254, 1173, 1104, 834, 775 cm^{-1}; **HRMS** (DART) Calcd for $C_{29}H_{50}NO_5Si$ (MH^+): 520.3453; found: 520.3454.

3.21e-Minor: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 4H), 7.23 – 7.17 (m, 1H), 5.03 – 4.93 (m, 1H), 4.93 – 4.84 (m, 1H), 3.61 (dd, *J* = 10.3, 4.1 Hz, 1H), 3.55 (t, *J* = 5.2 Hz, 1H), 3.50 (d, *J* = 13.2 Hz, 1H), 3.36 (d, *J* = 13.2 Hz, 1H), 3.19 (dt, *J* = 12.2, 3.6 Hz, 1H), 2.86 (d, *J* = 11.2 Hz, 1H), 2.67 – 2.50 (m, 2H), 2.35 – 2.24 (m, 1H), 2.09 (d, *J* = 11.0 Hz, 1H), 1.95 (t, *J* = 11.5 Hz, 1H), 1.70 (dd, *J* = 21.8, 11.1 Hz, 3H), 1.54 (tt, *J* = 14.2, 7.1 Hz, 1H), 1.33 (dq, *J* = 11.0, 5.3 Hz, 1H), 1.20 (dd, *J* = 10.0, 6.3 Hz, 6H), 1.13 (d, *J* = 6.3 Hz, 3H), 1.03 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.04 (d, *J* = 5.8 Hz, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.7, 172.0, 138.3, 129.0, 128.1, 126.9, 125.5, 67.9, 67.8, 65.0, 63.3, 54.4, 53.9, 41.3, 39.8, 39.3, 31.0, 29.0, 25.95, 25.94, 21.8, 21.74, 21.70, 21.5, 18.3, -5.5, -5.5; **HRMS** (DART) Calcd for $C_{29}H_{50}NO_5Si$ (MH^+): 520.3453; found: 520.3436.



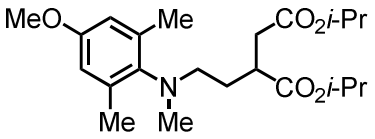
3.21f-major **3.21f-minor**

Diisopropyl 2-(1-benzyl-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,4,5,6-tetrahydropyridin-3-yl)succinate (3.21f)

^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio of **3.21f** was 1.4:1. After purification by column chromatography (ethyl ether:hexanes = 1:9), **3.21f** was obtained as a mixture of diastereomers (26.9 mg, 26%). Further purification was carried out by PTLC using ethyl ether:DCM = 1:49 as the eluent to separate **3.21f-major** and **3.21f-minor**. The relative configuration of **3.21f-major** and **3.21f-minor** was assigned in analogy (see **Section 3.6.3**).

3.21f-Major: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.4 Hz, 2H), 7.27 – 7.21 (m, 1H), 7.19 (d, *J* = 7.5 Hz, 2H), 6.06 (s, 1H), 5.05 – 4.90 (m, 2H), 4.08 – 3.89 (m, 2H), 3.57 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.29 (dd, *J* = 10.0, 5.7 Hz, 1H), 3.21 (t, *J* = 9.9 Hz, 1H), 2.87 (dd, *J* = 16.4, 10.1 Hz, 1H), 2.79 – 2.64 (m, 2H), 2.45 (dd, *J* = 16.3, 5.7 Hz, 1H), 2.37 (d, *J* = 7.8 Hz, 1H), 1.95 (dt, *J* = 13.4, 2.8 Hz, 1H), 1.65 – 1.46 (m, 1H), 1.32 – 1.11 (m, 12H), 0.86 (s, 9H), 0.06 – -0.08 (m, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.8, 171.6, 138.4, 135.5, 128.3, 127.8, 127.1, 102.6, 67.73, 67.66, 65.0, 59.3, 44.3, 41.8, 36.4, 36.3, 26.0, 25.94, 25.90, 23.2, 21.84, 21.82, 21.77, 21.75, 21.7, 18.3, -5.2, -5.4; **IR** (neat) ν 2950, 2854, 1726, 1676, 1466, 1372, 1256, 1172, 1143, 1105, 836 cm^{-1}; **HRMS** (DART) Calcd for $C_{29}H_{48}NO_5Si$ (MH^+): 518.3296; found: 518.3284.

3.21f-Minor: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 – 7.20 (m, 3H), 7.20 – 7.14 (m, 2H), 6.09 (s, 1H), 5.05 – 4.88 (m, 2H), 3.99 (d, *J* = 3.7 Hz, 2H), 3.78 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.26 (dd, *J* = 10.0, 5.5 Hz, 1H), 3.19 (t, *J* = 10.1 Hz, 1H), 2.87 – 2.74 (m, 2H), 2.74 – 2.62 (m, 1H), 2.48 (dd, *J* = 16.5, 5.5 Hz, 1H), 2.22 – 2.08 (m, 1H), 1.99 (dd, *J* = 13.6, 2.9 Hz, 1H), 1.67 – 1.59 (m, 1H), 1.27 – 1.16 (m, 12H), 0.88 (s, 9H), 0.03 (d, *J* = 8.5 Hz, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.4, 171.6, 138.3, 135.5, 128.3, 127.8, 127.1, 103.0, 67.7, 67.6, 65.3, 59.3, 45.0, 41.6, 38.5, 37.6, 26.0, 23.2, 21.9, 21.8, 21.6, 18.3, -5.2, -5.4; **HRMS** (DART) Calcd for $C_{29}H_{48}NO_5Si$ (MH^+): 518.3296; found: 518.3283.

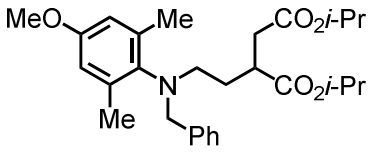


3.21g

Diisopropyl 2-(2-((4-methoxy-2,6-dimethylphenyl)(methyl)amino)ethyl)succinate (3.21g)

N-Ethyl-4-methoxy-*N*,2,6-trimethylaniline **3.19e** was reacted with diisopropyl fumarate **2.20a** following the **General Procedure C** using $B(C_6F_5)_3$ (10 mol%) as the Lewis acid catalyst and benzene (0.2 mL) as the solvent. After purification by column chromatography (ethyl ether:hexanes = 1:33) **3.21g** was obtained as a colorless liquid (76 mg, 97%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.52 (s, 2H), 4.99 (dqd, *J* = 12.5, 6.3, 1.6 Hz, 2H), 3.74 (d, *J* = 1.5 Hz, 3H), 3.05 – 2.96 (m, 2H), 2.93 – 2.85 (m, 1H), 2.71 (s, 2H), 2.63 (ddd, *J* = 16.4, 9.2, 1.5 Hz, 1H), 2.37 (dd, *J* = 16.4, 5.4 Hz, 1H), 2.25 (d, *J* = 7.6 Hz, 6H), 1.81 (dt, *J* = 15.4, 7.7 Hz, 1H), 1.62 (dq, *J* = 14.9, 8.4, 7.4 Hz, 1H), 1.21 (ddd, *J* = 7.8, 4.6, 1.5 Hz, 9H), 1.17 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.3, 171.3, 156.3, 142.2, 138.5, 138.4, 113.6, 67.9, 67.79, 67.77, 67.7, 55.1, 55.1, 53.2, 40.4, 40.3, 39.2, 36.5, 31.4, 21.7, 21.6, 19.4; **IR** (neat) ν 2976, 2932, 1724, 1601, 1485, 1372, 1170, 1104, 1062, 854 cm^{-1}; **HRMS** (DART) Calcd for $C_{22}H_{36}NO_5$ (MH^+): 394.2588; found: 394.2582.

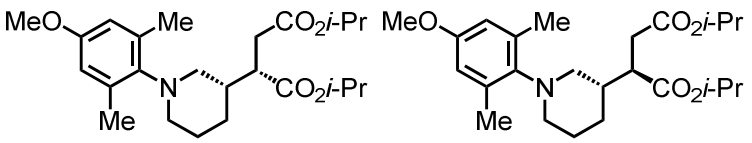


3.21h

Diisopropyl 2-(2-(benzyl(4-methoxy-2,6-dimethylphenyl)amino)ethyl)succinate (3.21h)

N-Benzyl-*N*-ethyl-4-methoxy-2,6-dimethylaniline **3.19f** was reacted with diisopropyl fumarate **2.20a** following the **General Procedure C** using $B(C_6F_5)_3$ (10 mol%) as the Lewis acid catalyst and benzene (0.2 mL) as the solvent. After purification by column chromatography (ethyl ether:hexanes = 1:33) **3.21h** was obtained as a colorless liquid (82 mg, 87%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 – 7.19 (m, 5H), 6.53 (s, 2H), 4.93 (dp, *J* = 12.5, 6.3 Hz, 2H), 4.09 (s, 2H), 3.74 (s, 3H), 3.00 (ddd, *J* = 9.6, 6.2, 3.4 Hz, 2H), 2.71 (dq, *J* = 13.6, 6.1 Hz, 1H), 2.54 (dd, *J* = 16.3, 9.4 Hz, 1H), 2.27 – 2.18 (m, 7H), 1.68 (ddd, *J* = 16.9, 13.9, 7.3 Hz, 1H), 1.50 (ddd, *J* = 13.3, 9.4, 6.5 Hz, 1H), 1.19 – 1.14 (m, 9H), 1.10 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.1, 171.2, 156.5, 140.4, 139.9, 138.9, 138.8, 128.8, 128.1, 126.8, 113.87, 113.85, 113.81, 113.79, 67.8, 58.9, 55.11, 55.05, 50.2, 39.5, 36.4, 31.1, 21.70, 21.67, 21.64, 21.56, 20.0, 19.9; **IR** (neat) ν 2976, 2934, 1725, 1601, 1466, 1372, 1312, 1195, 1105, 670 cm^{-1}; **HRMS** (DART) Calcd for $C_{28}H_{40}NO_5$ (MH^+): 470.2901; found: 470.2896.



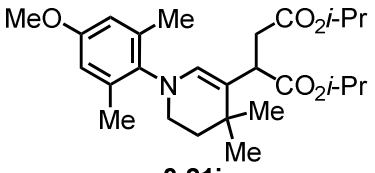
3.21i-major **3.21i-minor**

Diisopropyl 2-(1-(4-methoxy-2,6-dimethylphenyl)piperidin-3-yl)succinate (3.21i)

1-(4-Methoxy-2,6-dimethylphenyl)piperidine **3.19g** was reacted with diisopropyl fumarate **2.20a** following the **General Procedure C** using $B(C_6F_5)_3$ (5.0 mol%) as the Lewis acid catalyst and benzene (0.8 mL) as the solvent. ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was 1.3:1. After purification by column chromatography (ethyl ether:hexanes = 1:19) **3.21i** was obtained as a mixture of diastereomers (75 mg, 89%). Further purification was carried out by PTLC using ethyl ether:DCM = 1:49 as the eluent to separate **3.21i-major** and **3.21i-minor**. The relative configuration of **3.21i-major** and **3.21i-minor** was assigned in analogy (see **Section 3.6.3**).

3.21i-Major: ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 6.57 (d, *J* = 3.0 Hz, 1H), 6.46 (d, *J* = 3.1 Hz, 1H), 5.04 (hept, *J* = 5.9 Hz, 1H), 4.96 (hept, *J* = 12.6, 6.3 Hz, 1H), 3.74 (s, 3H), 3.02 (td, *J* = 11.2, 2.9 Hz, 1H), 2.90 (d, *J* = 7.0 Hz, 2H), 2.85 (dt, *J* = 11.8, 3.8 Hz, 1H), 2.77 – 2.63 (m, 2H), 2.44 – 2.37 (m, 1H), 2.26 (s, 3H), 2.24 (s, 3H), 1.96 – 1.85 (m, 1H), 1.78 (dt, *J* = 13.0, 3.9 Hz, 1H), 1.72 (dt, *J* = 12.7, 3.5 Hz, 1H), 1.68 – 1.55 (m, 2H), 1.25 (t, *J* = 6.2 Hz, 6H), 1.19 (dd, *J* = 7.6, 6.2 Hz, 6H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 173.7, 171.6, 156.3, 142.4, 138.7, 137.9, 114.0, 113.3, 67.9, 67.8, 55.2, 54.6, 50.7, 44.9, 39.5, 34.5, 28.5, 26.5, 21.9, 21.8, 21.7, 19.9, 19.5; **IR** (neat) ν 2976, 2932, 1727, 1485, 1372, 1220, 1173, 1156, 1106, 1067 cm^{-1}; **HRMS** (DART) Calcd for $C_{24}H_{38}NO_5$ (MH^+): 420.2745; found: 420.2741.

3.21i-Minor: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.56 (d, *J* = 3.0 Hz, 1H), 6.45 (d, *J* = 3.1 Hz, 1H), 4.99 (dq, *J* = 11.8, 6.1 Hz, 2H), 3.74 (s, 3H), 3.02 (td, *J* = 11.2, 2.6 Hz, 1H), 2.93 – 2.86 (m, 2H), 2.84 (dt, *J* = 11.9, 3.9 Hz, 1H), 2.76 – 2.64 (m, 2H), 2.46 (dd, *J* = 15.7, 3.4 Hz, 1H), 2.26 (s, 3H), 2.24 (s, 3H), 1.92 (dq, *J* = 11.6, 6.2 Hz, 1H), 1.84 (dd, *J* = 13.1, 3.7 Hz, 1H), 1.73 – 1.56 (m, 3H), 1.25 (t, *J* = 7.0 Hz, 1H), 1.21 (dd, *J* = 6.2, 2.6 Hz, 9H), 1.17 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.4, 171.7, 156.2, 142.5, 138.7, 137.7, 114.0, 113.2, 67.9, 67.8, 55.2, 54.7, 50.8, 45.0, 39.5, 34.5, 28.6, 26.6, 21.81, 21.80, 21.76, 20.0, 19.5; **HRMS** (DART) Calcd for $C_{24}H_{38}NO_5$ (MH^+): 420.2745; found: 420.2734.

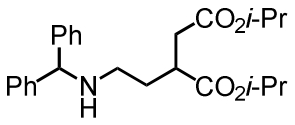


3.21j

Diisopropyl 2-(1-(4-methoxy-2,6-dimethylphenyl)-4,4-dimethylpiperidin-3-yl)succinate (3.21j)

1-(4-Methoxy-2,6-dimethylphenyl)-4,4-dimethylpiperidine **3.19h** was reacted with diisopropyl fumarate **2.20a** following the **General Procedure D** using $B(C_6F_5)_3$ (10 mol%) as the Lewis acid catalyst, DCM (0.1 mL) as the solvent, and a second batch of **2.20a** in DCM (0.05 mL) was added. After purification by column chromatography (ethyl ether:hexanes = 1:33) **3.21j** was obtained as a colorless liquid (89 mg, 93%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.55 (d, *J* = 13.5 Hz, 2H), 5.82 (s, 1H), 4.96 (dp, *J* = 17.2, 6.3 Hz, 2H), 3.75 (s, 3H), 3.41 (dd, *J* = 10.9, 4.6 Hz, 1H), 3.22 (ddd, *J* = 12.3, 8.9, 3.7 Hz, 1H), 3.11 (ddd, *J* = 11.9, 6.4, 4.0 Hz, 1H), 2.78 (dd, *J* = 16.8, 10.9 Hz, 1H), 2.40 (dd, *J* = 16.7, 4.7 Hz, 1H), 2.18 (s, 3H), 2.13 (s, 3H), 1.76 (ddd, *J* = 12.9, 8.9, 4.0 Hz, 1H), 1.70 (ddd, *J* = 12.9, 6.4, 3.7 Hz, 1H), 1.23 (d, *J* = 6.3 Hz, 3H), 1.21 (d, *J* = 3.5 Hz, 3H), 1.20 (d, *J* = 3.5 Hz, 3H), 1.19 (s, 3H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.11 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.5, 171.8, 157.3, 138.8, 138.3, 138.2, 132.0, 113.4, 113.3, 108.1, 67.6, 67.3, 55.3, 44.1, 39.9, 39.6, 39.2, 31.6, 29.1, 28.2, 21.9, 21.82, 21.80, 21.5, 18.4, 18.3; **IR** (neat) ν 2977, 2933, 1723, 1639, 1466, 1259, 1162, 1102, 1065 cm^{-1}; **HRMS** (ESI) Calcd for $C_{26}H_{40}NO_5$ (MH^+): 446.2901; found: 446.2906.

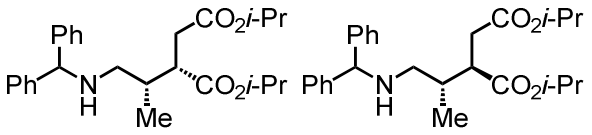


3.21K

Diisopropyl 2-(2-(benzhydrylamino)ethyl)succinate (3.21k)

N-Benzhydrylethanamine **3.19i** was reacted with diisopropyl fumarate **2.20a** following the **General Procedure D** using 10 mol% $B(C_6F_5)_3$ as the Lewis acid catalyst, benzene as the solvent. After purification by column chromatography (EtOAc:hexanes = 1:19) **3.21k** was obtained as a colorless liquid (77 mg, 93%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 4H), 7.28 (td, *J* = 7.5, 1.5 Hz, 4H), 7.22 – 7.16 (m, 2H), 4.98 (h, *J* = 6.3 Hz, 2H), 4.78 (s, 1H), 2.91 (ddt, *J* = 8.9, 7.5, 5.8 Hz, 1H), 2.68 – 2.55 (m, 3H), 2.37 (dd, *J* = 16.4, 5.4 Hz, 1H), 1.91 – 1.80 (m, 1H), 1.77 – 1.66 (m, 1H), 1.22 (d, *J* = 2.5 Hz, 3H), 1.20 (d, *J* = 2.5 Hz, 3H), 1.19 (d, *J* = 6.2 Hz, 3H), 1.14 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.2, 171.3, 144.0, 144.0, 128.4, 127.2, 126.4, 67.9, 67.5, 45.4, 39.5, 36.4, 32.2, 21.8, 21.74, 21.68, 21.6; **IR** (neat) ν 2977, 2933, 1727, 1452, 1373, 1265, 1173, 1105, 745, 703 cm^{-1}; **HRMS** (DART) Calcd for $C_{25}H_{34}NO_4$ (MH^+): 412.2482; found: 412.2478.



3.21l-major **3.21l-minor**

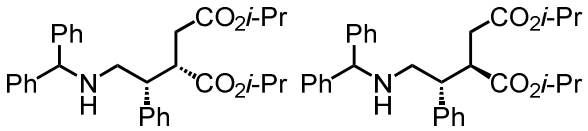
Diisopropyl 2-(1-(benzhydrylamino)propan-2-yl)succinate (3.21l)

N-Benzhydrylpropan-1-amine **3.19j** was reacted with diisopropyl fumarate **2.20a** following the **General Procedure C** using $B(C_6F_5)_3$ (10 mol%) as the Lewis acid catalyst and benzene (0.2 mL) as the solvent. ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was 1.1:1. After purification by column chromatography (EtOAc:hexanes = 1:19) **3o** was obtained as a mixture of diastereomers (56 mg, 66%). Further purification was carried out by PTLC using ethyl ether:DCM = 1:49 as the eluent to separate **3.21l-major** and **3.21l-minor**. The relative configuration of **3.21l-major** and **3.21l-minor** was assigned in analogy, see **Section 3.6.3**.

3.21l-Major: ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 4H), 7.28 (q, *J* = 7.8 Hz, 4H), 7.22 – 7.17 (m, 2H), 5.00 (dq, *J* = 12.2, 6.2 Hz, 2H), 4.76 (s, 1H), 3.13 (ddd, *J* = 11.1, 4.7, 3.6 Hz, 1H), 2.58 (dd, *J* = 16.6, 11.1 Hz, 1H), 2.49 (dd, *J* = 11.9, 6.6 Hz, 1H), 2.42 (dd, *J* = 11.9, 7.4 Hz, 1H), 2.19 (dd, *J* = 16.6, 3.6 Hz, 1H), 2.13 (pd, *J* = 7.0, 4.6 Hz, 1H), 1.25 – 1.20 (m, 9H), 1.17 (d, *J* = 6.2 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 174.1, 172.0, 144.2, 144.0, 128.5, 128.4, 127.3, 127.2, 127.0, 67.8, 67.6, 51.8, 43.6, 35.3, 31.5, 21.83, 21.80, 21.78, 21.7, 14.6; **IR** (neat) ν 2976, 2930, 1725, 1452, 1373, 1260, 1173, 1105, 745, 703 cm^{-1}; **HRMS** (DART) Calcd for $C_{26}H_{36}NO_4$ (MH^+): 426.2639; found: 426.2638.

3.21l-Minor: ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.3 Hz, 4H), 7.31 – 7.26 (m, 4H), 7.22 – 7.16 (m, 2H), 4.98 (pd, *J* = 6.3, 2.4 Hz, 2H), 4.75 (s, 1H), 2.97 (dt, *J* = 10.6, 4.3 Hz, 1H), 2.71 (dd, *J* = 16.6, 10.7 Hz, 1H), 2.57 (dd, *J* = 12.0, 7.0 Hz, 1H), 2.45 (dd, *J* = 12.0, 6.7 Hz, 1H), 2.27 (dd,

J = 16.5, 4.2 Hz, 1H), 2.00 (qd, *J* = 7.0, 4.6 Hz, 1H), 1.22 (t, *J* = 6.2 Hz, 6H), 1.19 (d, *J* = 6.3 Hz, 3H), 1.13 (d, *J* = 6.3 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.3, 171.9, 144.2, 144.1, 128.43, 128.41, 127.3, 127.2, 126.96, 126.95, 67.8, 67.7, 51.9, 44.0, 35.8, 34.0, 21.82, 21.81, 21.77, 21.7, 15.5; **HRMS** (DART) Calcd for $C_{26}H_{36}NO_4$ (MH^+): 426.2639; found: 426.2626.



3.21m-major **3.21m-minor**

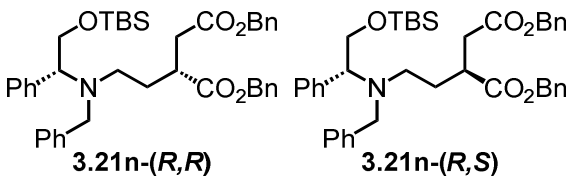
Diisopropyl 2-(2-(benzhydrylamino)-1-phenylethyl)succinate (3.21m)

N-Benzhydryl-2-phenylethan-1-amine **3.19k** was reacted with diisopropyl fumarate **2.20a** following the **General Procedure C** using $B(C_6F_5)_3$ (10 mol%) as the Lewis acid catalyst and benzene (0.2 mL) as the solvent. ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was 2.1:1. After purification by column chromatography (EtOAc:hexanes = 1:19) **3.21m** was obtained as a mixture of diastereomers (85 mg, 87%). Further purification was carried out by PTLC using ethyl ether:DCM = 1:49 as the eluent to separate **3.21m-major** and **3.21m-minor**. The relative configuration of **3.21m-major** and **3.21m-minor** was assigned in analogy, see **Section 3.6.3**.

3.21m-Major: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.4 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.25 – 7.19 (m, 6H), 7.19 – 7.12 (m, 4H), 4.89 (dhept, *J* = 12.5, 6.2 Hz, 2H), 4.71 (s, 1H), 3.06 (qd, *J* = 9.5, 8.5, 3.9 Hz, 2H), 2.87 (dd, *J* = 12.0, 8.5 Hz, 1H), 2.81 (dd, *J* = 12.0, 4.6 Hz, 1H), 2.47 (dd, *J* = 16.8, 10.7 Hz, 1H), 2.08 (dd, *J* = 16.7, 2.9 Hz, 1H), 1.15 (d, *J* = 6.2 Hz, 3H), 1.13 (d, *J* = 6.3 Hz, 6H), 1.04 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.6, 171.3, 144.0, 143.8, 140.1, 128.8, 128.40, 128.35, 127.3, 127.18, 127.16, 126.94, 126.88, 68.1, 67.9, 67.2, 50.9, 48.1, 45.5, 35.3, 21.8, 21.69, 21.66, 21.5; **IR** (neat) ν 2976, 2931, 1725, 1451, 1372, 1263, 1170, 1105, 745, 700 cm^{-1}; **HRMS** (DART) Calcd for $C_{31}H_{38}NO_4$ (MH^+): 488.2795; found: 488.2772.

3.21m-Minor: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.1 Hz, 2H), 7.29 – 7.19 (m, 9H), 7.19 – 7.13 (m, 4H), 4.93 (p, *J* = 6.2 Hz, 1H), 4.79 (p, *J* = 6.3 Hz, 1H), 4.74 (s, 1H), 3.21 – 3.10 (m,

2H), 2.95 – 2.85 (m, 2H), 2.60 (dd, J = 16.6, 10.4 Hz, 1H), 2.33 (dd, J = 16.6, 3.8 Hz, 1H), 1.18 (t, J = 6.9 Hz, 6H), 1.08 (d, J = 6.2 Hz, 3H), 0.91 (d, J = 6.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.8, 171.4, 143.9, 140.0, 128.6, 128.43, 128.40, 127.3, 127.2, 127.1, 127.0, 126.9, 67.92, 67.88, 67.4, 49.5, 47.7, 45.5, 34.4, 21.8, 21.7, 21.6, 21.3; **HRMS** (DART) Calcd for $C_{31}H_{38}NO_4$ (MH^+): 488.2795; found: 488.2791.



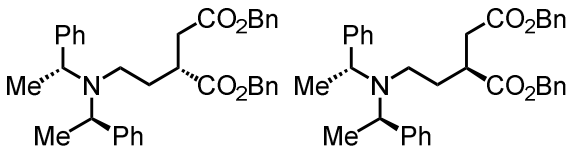
3.21n-(*R,R*) **3.21n-(*R,S*)**

Dibenzyl 2-(2-(benzyl((*R*)-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethyl)amino)ethyl) succinate (3.21n)

(*R*)-*N*-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-*N*-ethyl-1-phenylethan-1-amine **3.19l** was reacted with dibenzyl fumarate **2.20b** following the **General Procedure C** using $B(C_6F_5)_3$ (10 mol%) as the Lewis acid catalyst and benzene (0.8 mL) as the solvent. After purification by column chromatography (ethyl ether:hexanes = 1:19) **3.21n** was obtained as a mixture of diastereomers (93 mg, 69%, dr = 1.5:1). Further purification was carried out by PTLC using ethyl ether:DCM = 1:49 as the eluent to separate **3.21n-(*R,R*)** and **3.21n-(*R,S*)**. The absolute configuration of **3.21n-(*R,R*)** was assigned in analogy to **3.21o-(*R,R*)** (see **Section 3.6.4**).

3.21n-(*R,R*): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 – 7.13 (m, 18H), 7.10 (q, *J* = 6.9 Hz, 2H), 4.97 (d, *J* = 12.4 Hz, 1H), 4.95 – 4.89 (m, 3H), 3.98 (dd, *J* = 10.5, 6.2 Hz, 1H), 3.87 (dd, *J* = 10.5, 6.1 Hz, 1H), 3.75 (t, *J* = 6.1 Hz, 1H), 3.64 (d, *J* = 14.0 Hz, 1H), 3.51 (d, *J* = 14.0 Hz, 1H), 2.89 (dq, *J* = 11.9, 6.4 Hz, 1H), 2.64 (dt, *J* = 13.5, 6.3 Hz, 1H), 2.43 (dd, *J* = 16.6, 9.5 Hz, 1H), 2.37 (dt, *J* = 13.9, 7.4 Hz, 1H), 2.06 (dd, *J* = 16.7, 4.7 Hz, 1H), 1.81 (dq, *J* = 14.1, 7.1 Hz, 1H), 1.46 (dq, *J* = 13.8, 6.9 Hz, 1H), 0.76 (s, 9H), -0.10 (d, *J* = 5.1 Hz, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.8, 171.5, 140.5, 140.1, 135.9, 135.8, 128.69, 128.65, 128.5, 128.4, 128.21, 128.17, 128.14, 128.11, 128.06, 127.90, 126.85, 126.7, 66.33, 66.27, 64.5, 63.2, 55.0, 47.4, 38.6, 35.4, 29.7, 25.8, 18.2, 1.0, -5.48, -5.50; **IR** (neat) ν 2925, 2853, 1733, 1453, 1253, 1152, 1106, 835, 746, 697 cm^{-1}; $[\alpha]^{25}_D$ = – 26.6° (c = 0.6, EtOH); **HRMS** (DART) Calcd for $C_{41}H_{52}NO_5Si$ (MH^+): 666.3609; found: 666.3600.

3.21n-(*R,S*): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 19H), 7.16 (t, *J* = 7.3 Hz, 1H), 5.04 (d, *J* = 12.3 Hz, 1H), 5.02 – 4.97 (m, 3H), 4.03 (dd, *J* = 10.4, 6.3 Hz, 1H), 3.89 (dd, *J* = 10.5, 6.2 Hz, 1H), 3.85 – 3.77 (m, 2H), 3.42 (d, *J* = 14.1 Hz, 1H), 2.96 (dq, *J* = 12.3, 6.0 Hz, 1H), 2.60 (dt, *J* = 13.4, 7.7 Hz, 1H), 2.52 (dd, *J* = 16.6, 9.4 Hz, 1H), 2.44 (ddd, *J* = 13.2, 8.2, 4.8 Hz, 1H), 2.23 (dd, *J* = 16.7, 4.8 Hz, 1H), 1.92 (dq, *J* = 14.1, 7.3 Hz, 1H), 1.57 – 1.48 (m, 1H), 0.81 (s, 9H), -0.06 (d, *J* = 5.6 Hz, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.7, 171.6, 140.6, 139.6, 135.9, 135.8, 128.7, 128.6, 128.5, 128.4, 128.22, 128.17, 128.13, 128.11, 128.06, 127.9, 127.0, 126.7, 66.32, 66.29, 65.4, 64.0, 55.1, 47.6, 38.6, 35.3, 30.3, 29.7, 29.4, 25.8, 18.2, -5.51, -5.53; **HRMS** (DART) Calcd for $C_{41}H_{52}NO_5Si$ (MH^+): 666.3609; found: 666.3595.



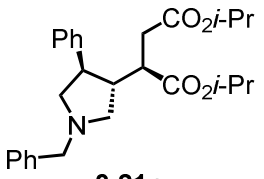
3.21o-(*R,R,R*) **3.21o-(*R,R,S*)**

Dibenzyl 2-(2-(bis((*R*)-1-phenylethyl)amino)ethyl)succinate (3.21o)

(*R*)-*N*-Ethyl-1-phenyl-*N*-((*R*)-1-phenylethyl)ethan-1-amine **3.19m** was reacted with dibenzyl fumarate **2.20b** following the **General Procedure C** using $B(C_6F_5)_3$ (10 mol%) as the Lewis acid catalyst and benzene (0.8 mL) as the solvent. ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was 1.4:1. After purification by column chromatography (ethyl ether:hexanes = 1:9), **3.21o-(*R,R,R*)** (3.3 mg, 3% yield), **3.21o-mixture** (81 mg, 77%) and **3.21o-(*R,R,S*)** (2.2 mg, 2% yield) were obtained as colorless oils. The absolute configuration of product **3.21o-(*R,R,R*)** was assigned in analogy to a previously synthesized molecule (see **Section 3.74** for details).

3.21o-(*R,R,R*): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 18H), 7.20 – 7.14 (m, 2H), 5.03 (d, *J* = 12.4 Hz, 1H), 4.98 (d, *J* = 12.4 Hz, 1H), 4.94 (s, 2H), 3.93 (q, *J* = 6.8 Hz, 2H), 2.70 – 2.49 (m, 3H), 2.40 (ddd, *J* = 14.0, 10.5, 5.3 Hz, 1H), 2.19 (dd, *J* = 16.5, 4.9 Hz, 1H), 1.62 – 1.47 (m, 1H), 1.31 (d, *J* = 6.8 Hz, 6H), 1.28 – 1.15 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.3, 171.5, 144.9, 135.9, 135.7, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 126.6, 66.33, 66.29, 57.9, 44.0, 39.2, 36.0, 33.1, 18.2; **IR** (neat) ν 3027, 2965, 1729, 1492, 1452, 1258, 1211, 1150, 971, 736, 696 cm^{-1}; $[\alpha]^{25}_D$ = –3.1° (c = 0.9, EtOH); **HRMS** (DART) Calcd for $C_{36}H_{40}NO_4$ (MH^+): 550.2952; found: 550.2951.

3.21o-(*R*,*R*,*S*): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 14H), 7.23 (t, *J* = 7.5 Hz, 4H), 7.14 (t, *J* = 7.2 Hz, 2H), 5.04 – 4.93 (m, 4H), 3.95 (q, *J* = 7.1 Hz, 2H), 2.75 (dq, *J* = 11.4, 6.1 Hz, 1H), 2.59 (ddd, *J* = 14.2, 8.8, 5.1 Hz, 1H), 2.44 – 2.33 (m, 2H), 1.88 (dd, *J* = 16.8, 4.7 Hz, 1H), 1.57 – 1.49 (m, 1H), 1.33 (d, *J* = 6.9 Hz, 6H), 1.30 – 1.27 (m, 1H); **^{13}C NMR** δ 174.8, 171.6, 144.8, 135.9, 135.8, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 126.6, 66.3, 57.3, 43.0, 38.6, 35.1, 32.3, 17.3; **HRMS** (DART) Calcd for $C_{36}H_{40}NO_4$ (MH^+): 550.2952; found: 550.2967.



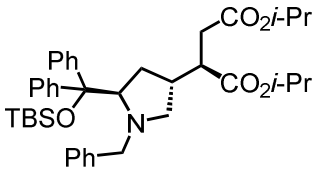
3.21p

Diisopropyl 2-((4*R*)-1-benzyl-4-phenylpyrrolidin-3-yl)succinate (3.21p)

(*R*)-1-Benzyl-3-phenylpyrrolidine **3.19n** was reacted with diisopropyl fumarate **2.20a** following the **General Procedure C** using $B(C_6F_5)_3$ (10 mol%) as the Lewis acid catalyst and benzene (0.2 mL) as the solvent. ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was 1.6:1. After purification by column chromatography (ethyl ether:hexanes = 1:4), **3.21p** was obtained as a mixture of diastereomers (78.7 mg, 90%). Further purification was carried out by PTLC using ethyl ether:DCM:hexanes = 2:8:3 as the eluent to separate **3.21p-(*R*,*R*,*R*)** and **3.21p-minor**. The absolute configuration of **3.21p-(*R*,*R*,*R*)** was assigned based on analogy to **3.21q-(*R*,*R*,*R*)** and by NOESY experiments (see **Section 3.6.3** for NOE spectra).

3.21p-(*R*,*R*,*R*): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 (ddt, *J* = 19.6, 15.2, 4.7 Hz, 8H), 7.23 (d, *J* = 6.9 Hz, 1H), 7.18 (d, *J* = 6.9 Hz, 1H), 4.99 – 4.82 (m, 2H), 3.64 (d, *J* = 12.9 Hz, 1H), 3.57 (d, *J* = 12.9 Hz, 1H), 3.17 – 3.10 (m, 1H), 2.96 – 2.88 (m, 2H), 2.85 (t, *J* = 8.6 Hz, 1H), 2.70 – 2.61 (m, 1H), 2.61 – 2.55 (m, 2H), 2.55 – 2.48 (m, 1H), 2.40 (dd, *J* = 16.8, 3.9 Hz, 1H), 1.21 – 1.14 (m, 9H), 1.02 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.0, 171.5, 145.0, 139.0, 128.6, 128.5, 128.2, 127.7, 126.9, 126.3, 68.0, 67.9, 63.3, 60.2, 58.1, 48.7, 47.7, 44.7, 34.9, 21.78, 21.75, 21.7, 21.5; **IR** (neat) ν 2975, 2932, 2788, 1725, 1492, 1372, 1261, 1173, 1144, 1105, 754, 699 cm^{-1}; **$[\alpha]^{25}_D$** = 5.1° (c = 0.9, EtOH); **HRMS** (DART) Calcd for $C_{27}H_{36}NO_4$ (MH^+): 438. 2639; found: 438.2627.

3.21p-Minor: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 – 7.22 (m, 8H), 7.17 (q, *J* = 7.0 Hz, 2H), 4.99 – 4.91 (m, 1H), 4.82 – 4.70 (m, 1H), 3.61 (d, *J* = 7.9 Hz, 2H), 3.17 (t, *J* = 7.0 Hz, 1H), 2.88 (dq, *J* = 24.7, 8.0, 7.6 Hz, 3H), 2.69 – 2.53 (m, 3H), 2.47 (t, *J* = 8.1 Hz, 1H), 2.37 (dd, *J* = 16.9, 3.9 Hz, 1H), 1.21 – 1.16 (m, 6H), 1.12 (d, *J* = 6.3 Hz, 3H), 0.95 (d, *J* = 6.3 Hz, 3H); **HRMS** (DART) Calcd for $C_{27}H_{36}NO_4$ (MH^+): 438. 2639; found: 438.2639.



3.21q

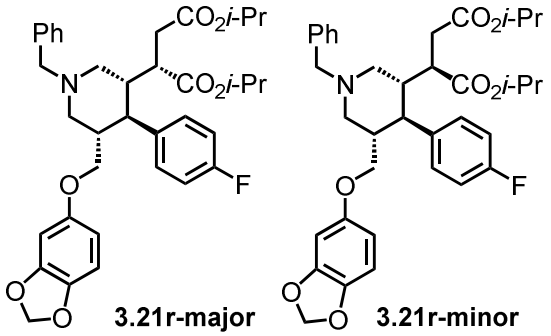
Diisopropyl 2-((5*R*)-1-benzyl-5-(((*tert*-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidin -3-yl)succinate (3.21q)

(*R*)-1-Benzyl-2-(((*tert*-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine **3.19o** was reacted with diisopropyl fumarate **2.20a** following the **General Procedure C** using $B(C_6F_5)_3$ (10 mol%) as the Lewis acid catalyst and benzene (0.2 mL) as the solvent. ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was 2.5:1. After purification by column chromatography (ethyl ether:hexanes = 1:9) **3.21q** was obtained as a mixture of diastereomers (74 mg, 56%). Further purification was carried out by PTLC using ethyl ether:DCM = 1:49 as the eluent to separate **3.21q-(*R,R,R*)** and **3.21q-minor**. The absolute configuration of **3.21q-(*R,R,R*)** was assigned based on X-ray crystallography data (see **Sections 3.6.4**).

3.21q-(*R,R,R*): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (s, 2H), 7.55 (d, *J* = 7.3 Hz, 2H), 7.35 – 7.26 (m, 6H), 7.19 (t, *J* = 7.4 Hz, 2H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.04 (d, *J* = 7.4 Hz, 2H), 4.90 (p, *J* = 6.2 Hz, 1H), 4.78 (p, *J* = 5.9 Hz, 1H), 4.41 (br, 1H), 4.01 (d, *J* = 10.1 Hz, 1H), 3.35 (d, *J* = 12.8 Hz, 1H), 2.46 (t, *J* = 7.8 Hz, 1H), 2.39 – 2.28 (m, 2H), 2.13 (d, *J* = 14.4 Hz, 1H), 1.98 (t, *J* = 10.1 Hz, 2H), 1.66 (q, *J* = 11.6 Hz, 2H), 1.15 (t, *J* = 5.8 Hz, 6H), 1.08 (d, *J* = 6.4 Hz, 3H), 0.94 (d, *J* = 6.3 Hz, 3H), 0.88 (s, 9H), -0.41 (s, 3H), -0.45 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.1, 171.3, 143.4, 140.3, 130.1, 129.9, 128.4, 128.0, 127.4, 127.2, 127.1, 126.4, 70.6, 67.9, 67.5, 61.8, 59.1, 45.0, 38.3, 35.4, 26.3, 21.8, 21.70, 21.67, 21.4, 19.0, -2.9, -3.0; **IR** (neat) ν 2975, 2927, 2853,

1727, 1372, 1254, 1173, 1105, 1060, 833, 774, 702 cm^{-1}; $[\alpha]^{25}_{D}$ = 43.1 ° (c = 0.7, EtOH); **HRMS** (DART) Calcd for $C_{40}H_{56}NO_5Si$ (MH^+): 658.3922; found: 658.3905.

3.21q-Minor: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 – 7.56 (m, 2H), 7.54 (d, *J* = 6.3 Hz, 2H), 7.37 – 7.27 (m, 6H), 7.22 (t, *J* = 7.5 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 2H), 4.90 (p, *J* = 6.3 Hz, 1H), 4.85 (p, *J* = 6.3 Hz, 1H), 4.45 (br, 1H), 4.05 (dd, *J* = 10.2, 2.6 Hz, 1H), 3.36 (d, *J* = 13.1 Hz, 1H), 2.58 (dd, *J* = 8.8, 6.4 Hz, 1H), 2.35 – 2.25 (m, 2H), 2.10 (s, 1H), 2.00 – 1.89 (m, 2H), 1.89 – 1.80 (m, 2H), 1.19 (d, *J* = 6.2 Hz, 3H), 1.15 (d, *J* = 6.3 Hz, 3H), 1.11 (d, *J* = 6.2 Hz, 3H), 1.09 (d, *J* = 6.2 Hz, 3H), 0.87 (s, 9H), -0.42 (s, 3H), -0.46 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.1, 171.2, 143.5, 140.4, 130.0, 129.9, 128.2, 128.1, 127.4, 127.2, 127.1, 126.7, 126.4, 70.8, 67.8, 67.7, 61.8, 59.5, 45.4, 38.4, 35.8, 33.5, 26.3, 21.8, 21.74, 21.70, 21.6, 18.9, -2.9, -3.0; **HRMS** (DART) Calcd for $C_{40}H_{56}NO_5Si$ (MH^+): 658.39223; found: 658.38954.



Diisopropyl 2-((4*R*,5*S*)-5-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-1-benzyl-4-(4-fluorophenyl)piperidin-3-yl)succinate (3.21r)

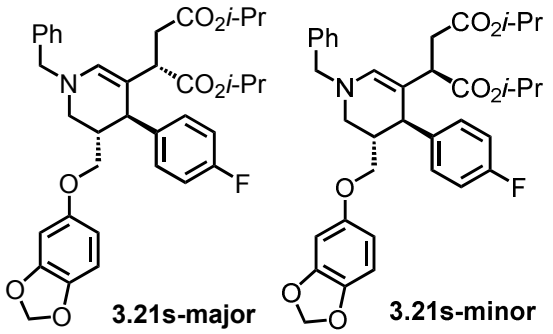
For 0.2 mmol scale:

(3*S*,4*R*)-3-((Benzo[*d*][1,3]dioxol-5-yloxy)methyl)-1-benzyl-4-(4-fluorophenyl)piperidine **3.19p** was reacted with diisopropyl fumarate **2.20a** following the **General Procedure D** using $B(C_6F_5)_3$ (10 mol%) as the Lewis acid catalyst and benzene as the solvent. ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio of **3.21r** was 2.3:1. After purification by column chromatography (ethyl ether:hexanes = 3:2), **3.21r** was obtained as a mixture of diastereomers (48 mg, 39%). The relative configuration of **3.21r-major** and **3.21r-minor** was assigned in analogy (see **Section 3.6.3**).

3.21r-Major: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.19 (m, 5H), 7.00 (s, 2H), 6.61 (d, J = 8.4 Hz, 1H), 6.31 (d, J = 2.5 Hz, 1H), 6.09 (dd, J = 8.5, 2.5 Hz, 1H), 5.88 (s, 2H), 4.94 – 4.76 (m, 2H), 3.64 (d, J = 13.1 Hz, 1H), 3.48 (d, J = 2.6 Hz, 1H), 3.45 (d, J = 13.1 Hz, 1H), 3.41 – 3.33 (m, 1H), 3.20 – 3.13 (m, 1H), 2.83 – 2.74 (m, 1H), 2.61 – 2.48 (m, 3H), 2.42 (t, J = 11.2 Hz, 1H), 2.29 – 2.17 (m, 2H), 2.13 (t, J = 11.1 Hz, 1H), 1.84 (t, J = 11.1 Hz, 1H), 1.15 (d, J = 6.2 Hz, 6H), 1.08 (d, J = 6.3 Hz, 3H), 1.02 (d, J = 6.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.3, 171.4, 161.8 (d, J_{C-F} = 245.3 Hz), 154.2, 148.1, 141.6, 137.9, 136.4, 136.3, 129.1, 128.2, 127.1, 115.8, 107.8, 105.6, 101.1, 97.9, 69.4, 68.1, 67.8, 63.3, 57.6, 54.7, 46.3, 43.2, 42.8, 41.5, 30.4, 21.71, 21.67, 21.6, 21.5;

^{19}F NMR (470 MHz, $CDCl_3$) δ -115.52, -115.53, -115.54, -115.55, -115.56, -115.58; **IR** (neat) ν 2978, 2917, 2870, 1724, 1508, 1502, 1486, 1224, 1182, 1104, 1037, 779 cm^{-1}; $[\alpha]^{25}_D$ = – 22.1° (c = 1.0, EtOH); **HRMS** (DART) Calcd for $C_{36}H_{43}FNO_7$ (MH^+): 620.3018; found: 620.3004.

3.21r-Minor: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 4H), 7.29 – 7.23 (m, 1H), 7.20 (t, *J* = 7.0 Hz, 2H), 6.98 (s, 2H), 6.60 (dd, *J* = 8.5, 1.7 Hz, 1H), 6.27 (t, *J* = 2.1 Hz, 1H), 6.06 (dt, *J* = 8.6, 2.1 Hz, 1H), 5.87 (d, *J* = 1.8 Hz, 2H), 4.97 (td, *J* = 6.3, 1.7 Hz, 1H), 4.88 (td, *J* = 6.2, 1.7 Hz, 1H), 3.58 (q, *J* = 13.2 Hz, 2H), 3.45 (dt, *J* = 9.4, 2.2 Hz, 1H), 3.40 – 3.23 (m, 1H), 3.19 – 3.09 (m, 1H), 3.09 – 2.97 (m, 1H), 2.83 – 2.64 (m, 2H), 2.64 – 2.51 (m, 1H), 2.25 – 2.08 (m, 3H), 2.05 (d, *J* = 11.1 Hz, 1H), 1.83 (t, *J* = 11.4 Hz, 2H), 1.30 (dd, *J* = 6.2, 1.7 Hz, 3H), 1.23 (dd, *J* = 6.3, 1.7 Hz, 3H), 1.15 (dt, *J* = 5.6, 2.3 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.1, 171.2, 161.7 (d, J_{C-F} = 244.8 Hz), 154.3, 148.1, 141.5, 137.8, 137.04, 137.02, 129.0, 128.3, 127.1, 115.5, 107.8, 105.4, 101.0, 97.8, 69.3, 68.1, 67.9, 63.3, 57.1, 55.6, 46.3, 44.2, 43.1, 40.9, 35.2, 22.0, 21.9, 21.73, 21.72; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -115.96, -115.98, -115.99, -116.00, -116.02; **HRMS** (DART) Calcd for $C_{36}H_{43}FNO_7$ (MH^+): 620.3018; found: 620.3001.



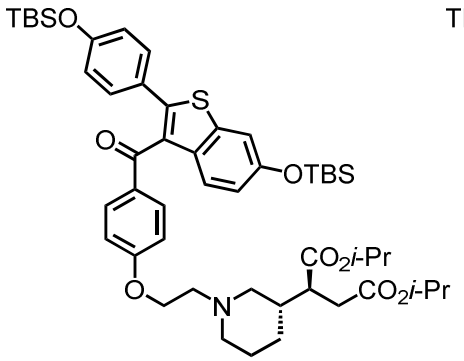
Diisopropyl 2-((4*R*,5*S*)-5-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-1-benzyl-4-(4-fluorophenyl)-1,4,5,6-tetrahydropyridin-3-yl)succinate (3.21s)

From 0.2 mmol of *N*-Bn paroxetine (3.21s): ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio of **3.21s** was 1.9:1. After purification by column chromatography (ethyl ether:hexanes = 1:4), **3.21s** was obtained as a mixture of diastereomers (19 mg, 14%). The relative configuration of **3.21s-major** and **3.21s-minor** was assigned in analogy (see **Section 3.6.3**).

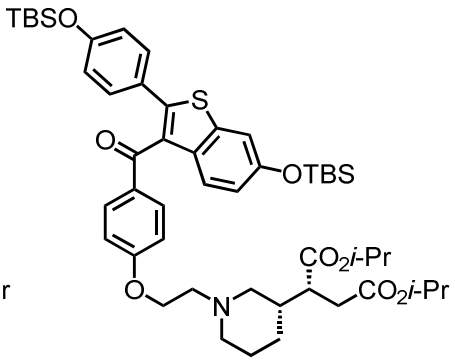
3.21s-Major: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 – 7.24 (m, 4H), 7.24 – 7.19 (m, 2H), 7.07 (s, 2H), 6.89 (s, 2H), 6.69 (d, J = 8.4 Hz, 1H), 6.43 (d, J = 2.4 Hz, 1H), 6.35 (s, 1H), 6.27 (dd, J = 8.5, 2.5 Hz, 1H), 5.91 (s, 2H), 5.00 – 4.83 (m, 2H), 4.17 – 3.99 (m, 2H), 3.78 (d, J = 23.9 Hz, 2H), 3.31 (s, 1H), 3.22 (dd, J = 10.3, 4.9 Hz, 1H), 2.81 – 2.67 (m, 2H), 2.56 (dd, J = 16.9, 10.3 Hz, 1H), 2.17 (dd, J = 16.9, 4.9 Hz, 1H), 2.09 – 1.99 (m, 1H), 1.21 (d, J = 6.2 Hz, 3H), 1.19 – 1.12 (m, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.0, 171.4, 161.5 (d, J_{C-F} = 244.4 Hz), 154.4, 148.2, 141.5 (d, J_{C-F} = 2.9 Hz), 137.6, 134.9, 129.9 (d, J_{C-F} = 7.7 Hz), 128.4, 128.1, 127.4, 114.8 (d, J_{C-F} = 21.1 Hz), 107.9, 105.9, 101.10, 101.07, 98.2, 70.2, 67.9, 67.8, 59.3, 45.9, 42.0, 40.8, 40.4, 37.4, 21.84, 21.78, 21.75, 21.7, 21.6; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -117.23, -117.24, -117.25, -117.26, -117.27, -117.28, -117.29; **IR** (neat) ν 2977, 2927, 2872, 1721, 1649, 1502, 1486, 1372, 1219, 1180, 1137,

1104, 817, 788, 701 cm^{-1}; $[\alpha]^{25}_{D} = -84.8°$ (c = 1.0, EtOH); **HRMS** (DART) Calcd for $C_{36}H_{41}FNO_7$ (MH^+): 618.2861; found: 618.2847.

3.21s-Minor: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 – 7.15 (m, 5H), 7.06 (dd, *J* = 8.3, 5.4 Hz, 2H), 6.89 (t, *J* = 8.5 Hz, 2H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.43 (d, *J* = 2.4 Hz, 1H), 6.30 (s, 1H), 6.26 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.98 – 5.84 (m, 2H), 4.92 (q, *J* = 6.3 Hz, 1H), 4.67 (q, *J* = 6.2 Hz, 1H), 4.09 (q, *J* = 14.6 Hz, 2H), 3.82 (dd, *J* = 9.1, 6.6 Hz, 1H), 3.75 (t, *J* = 8.3 Hz, 1H), 3.46 (s, 1H), 3.12 (dd, *J* = 10.5, 5.1 Hz, 1H), 2.90 (dd, *J* = 16.5, 10.6 Hz, 1H), 2.83 – 2.69 (m, 2H), 2.34 (dd, *J* = 16.5, 5.1 Hz, 1H), 2.07 (dd, *J* = 6.9, 3.8 Hz, 1H), 1.17 (d, *J* = 6.3 Hz, 6H), 1.10 (dd, *J* = 10.2, 6.3 Hz, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.1, 171.3, 161.5 (d, J_{C-F} = 244.5 Hz), 154.4, 148.2, 141.6, 140.9 (d, J_{C-F} = 3.1 Hz), 137.6, 134.7, 129.8 (d, J_{C-F} = 7.7 Hz), 128.5, 128.1, 127.5, 114.9 (d, J_{C-F} = 21.0 Hz), 107.9, 105.8, 101.8, 101.1, 98.2, 70.2, 68.0, 67.9, 59.5, 44.8, 42.4, 41.4, 40.5, 36.6, 21.79, 21.75, 21.60, 21.56; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -117.14, -117.15, -117.16, -117.17, -117.18, -117.19, -117.20 **HRMS** (DART) Calcd for $C_{36}H_{41}FNO_7$ (MH^+): 618.2861; found: 618.2859.



3.21t-major



3.21t-minor

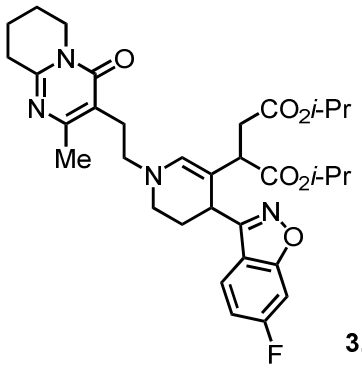
Diisopropyl 2-(1-(2-(4-(6-((*tert*-butyldimethylsilyl)oxy)-2-(4-((*tert*-butyldimethylsilyl) oxy)phenyl)benzo[*b*]thiophene-3-carbonyl)phenoxy)ethyl)piperidin-3-yl)succinate(3.21t)

(6-((*tert*-Butyldimethylsilyl)oxy)-2-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)benzo[*b*]thiophen -3-yl)(4-(2-(piperidin-1-yl)ethoxy)phenyl)methanone **3.19q** (0.20 mmol) was reacted with diisopropyl fumarate **2.20a** following the **General Procedure C** using $B(C_6F_5)_3$ (10 mol%) as the Lewis acid catalyst and benzene as the solvent. ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was 2.5:1. After purification by column chromatography (ethyl ether:DCM = 1:4), **3.21t** was obtained as a mixture of diastereomers (145 mg, 80%). Further purification was carried out by PTLC using MeOH:DCM = 1:49 as the eluent to separate **3.21t-major** and **3.21t-minor**. The relative configuration of **3.21t-major** and **3.21t-minor** was assigned in analogy (see **Section 3.6.3**).

3.21t-major. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.9 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.28 (d, *J* = 2.2 Hz, 1H), 7.27 – 7.25 (m, 1H), 7.25 – 7.23 (m, 1H), 6.88 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.72 (d, *J* = 8.9 Hz, 2H), 6.66 (d, *J* = 8.5 Hz, 2H), 4.99 (dp, *J* = 12.5, 6.3 Hz, 2H), 4.03 (t, *J* = 6.0 Hz, 2H), 2.87 (dd, *J* = 16.7, 9.2 Hz, 2H), 2.80 – 2.62 (m, 4H), 2.46 – 2.32 (m, 1H), 2.06 – 1.82 (m, 3H), 1.67 (dt, *J* = 16.5, 12.7 Hz, 2H), 1.54 (q, *J* = 12.8 Hz, 1H), 1.21 (td, *J* = 6.0, 1.8 Hz, 12H), 1.05 (dt, *J* = 10.5, 6.2 Hz, 1H), 1.01 (s, 9H), 0.93 (s, 9H), 0.23 (s, 6H), 0.12 (s, 6H). **^{13}C NMR**

(126 MHz, $CDCl_3$): δ 193.15, 173.16, 171.57, 162.81, 156.07, 153.48, 143.22, 139.84, 134.49, 132.28, 130.58, 130.50, 130.29, 126.75, 123.94, 120.24, 119.22, 114.02, 112.06, 67.99, 67.90, 66.08, 58.32, 57.39, 54.31, 45.06, 44.95, 38.14, 34.00, 27.84, 25.69, 25.62, 25.28, 21.80, 21.79, 21.74, 18.23, 18.18, -4.38, -4.48. **HRMS (DART):** Calcd for $C_{50}H_{72}NO_8SSi_2^+$ (MH^+): 902.4512; found: 902.4522.

3.21t-minor. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.28 (t, *J* = 1.8 Hz, 1H), 7.24 (d, *J* = 1.3 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 1H), 6.76 – 6.69 (m, 2H), 6.66 (d, *J* = 8.0 Hz, 2H), 5.06 – 4.93 (m, 2H), 4.03 (s, 2H), 2.93 – 2.81 (m, 2H), 2.79 – 2.66 (m, 4H), 2.37 (q, *J* = 10.0 Hz, 1H), 2.00 (t, *J* = 11.4 Hz, 1H), 1.94 (t, *J* = 10.9 Hz, 1H), 1.90 – 1.81 (m, 1H), 1.74 – 1.64 (m, 2H), 1.55 (d, *J* = 15.3 Hz, 1H), 1.20 (d, *J* = 1.7 Hz, 12H), 1.10 – 0.99 (m, 10H), 0.93 (s, 9H), 0.23 (s, 6H), 0.12 (s, 6H). **^{13}C NMR (151 MHz, $CDCl_3$):** δ 195.81, 175.86, 174.19, 165.45, 158.71, 156.13, 145.89, 142.49, 137.14, 134.94, 133.21, 133.15, 132.95, 129.40, 126.59, 122.90, 121.88, 116.65, 114.72, 70.65, 70.57, 68.74, 60.83, 60.02, 57.02, 47.60, 40.88, 36.89, 30.44, 28.34, 28.27, 27.81, 24.48, 24.45, 24.40, 20.88, 20.83, 2.63, -1.73, -1.83. **HRMS (DART):** Calcd for $C_{50}H_{72}NO_8SSi_2^+$ (MH^+): 902.4512; found: 902.4519.



3.21u

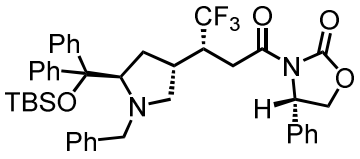
Diisopropyl 2-(4-(6-fluorobenzo[*d*]isoxazol-3-yl)-1-(2-(2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)ethyl)-1,4,5,6-tetrahydropyridin-3-yl)succinate (3.21u)

3-(2-(4-(6-Fluorobenzo[*d*]isoxazol-3-yl)piperidin-1-yl)ethyl)-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **3.19r** (1g, 2.4 mmol) was reacted with diisopropyl fumarate **3.20a** following the **General Procedure C** using $B(C_6F_5)_3$ (10 mol%) as the Lewis acid catalyst and DCM as the solvent. ^{1}H NMR analysis of the unpurified product mixture revealed that the diastereomeric ratio was 1.7:1. After purification by column chromatography (methanol:DCM = 1:49), **3.21u** was obtained as a mixture of diastereomers (470 mg, 32%). Further purification was carried out by PTLC using methanol:DCM = 1:49 as the eluent to separate **3.21u-major**.

3.21u-Major. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.21 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.06 – 7.00 (m, 1H), 6.15 (s, 1H), 4.95 – 4.81 (m, 1H), 4.81 – 4.68 (m, 1H), 4.08 (d, *J* = 5.1 Hz, 1H), 3.94 (t, *J* = 6.3 Hz, 2H), 3.22 – 3.12 (m, 3H), 3.10 (s, 2H), 2.89 (d, *J* = 6.9 Hz, 3H), 2.74 (d, *J* = 7.6 Hz, 2H), 2.40 (dd, *J* = 16.4, 4.8 Hz, 1H), 2.30 (s, 3H), 2.19 – 2.11 (m, 1H), 2.01 (d, *J* = 7.3 Hz, 1H), 1.98 (t, *J* = 6.2 Hz, 2H), 1.93 – 1.83 (m, 2H), 1.20 – 1.09 (m, 12H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 173.0, 171.3, 163.9, 163.2, 162.5, 161.3, 158.6, 156.2, 135.7, 135.6, 122.9, 122.8, 118.2, 118.0, 112.4, 112.2, 99.1, 97.3, 97.1, 67.9, 67.84, 67.80, 67.7, 53.3, 45.7, 44.5, 42.9, 42.8, 36.1, 31.7, 31.5, 29.7, 28.7, 28.4, 25.8, 22.0, 21.8, 21.74, 21.70, 21.62, 21.55, 21.5,

21.4, 19.2; **^{19}F NMR (470 MHz, $CDCl_3$):** δ -109.99; **IR (neat):** ν 2975, 2931, 1723, 1649, 1612, 1533, 1411, 1268, 1167, 1141, 1105, 919, 830 cm^{-1}; **HRMS (DART):** Calcd for $C_{33}H_{42}FN_4O_6$ (MH^+): 609.3083; found: 609.3072.

^{1}H NMR (500 MHz, $CDCl_3$, *peaks from diastereomers are merged*): δ 7.67 (dd, *J* = 9.0, 5.1 Hz, 1H), 7.22 (t, *J* = 6.8 Hz, 1H), 7.03 (q, *J* = 9.2 Hz, 1H), 6.24 – 6.10 (m, 1H), 4.88 (dt, *J* = 12.7, 6.4 Hz, 1H), 4.81 – 4.71 (m, 1H), 4.09 (dd, *J* = 5.8, 3.1 Hz, 1H), 3.94 (q, *J* = 5.0, 4.0 Hz, 2H), 3.27 – 3.04 (m, 5H), 2.87 (dt, *J* = 23.5, 9.0 Hz, 3H), 2.74 (t, *J* = 7.7 Hz, 2H), 2.64 – 2.35 (m, 1H), 2.31 (d, *J* = 3.9 Hz, 3H), 2.21 – 2.08 (m, 1H), 2.08 – 2.02 (m, 1H), 2.02 – 1.94 (m, 2H), 1.94 – 1.83 (m, 2H), 1.20 – 1.06 (m, 12H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 172.9, 172.8, 171.22, 171.16, 164.0 (d, *J* = 250.3 Hz), 164.0 (d, *J* = 250.3 Hz), 163.9, 163.8, 163.7, 162.4, 161.7, 161.2, 158.51, 158.47, 156.11, 156.07, 135.9, 135.6, 123.4 (d, *J* = 10.9 Hz), 122.8 (d, *J* = 11.0 Hz), 118.07, 118.05, 117.9, 117.6, 112.16 (d, *J* = 25.2 Hz), 112.22 (d, *J* = 25.1 Hz), 98.9, 98.5, 97.2 (d, *J* = 26.7 Hz). 97.1 (d, *J* = 26.7 Hz), 67.8, 67.7, 67.6, 53.2, 53.0, 45.6, 44.4, 42.9, 42.8, 42.6, 37.0, 36.0, 31.6, 31.38, 31.37, 31.1, 28.6, 28.4, 25.70, 25.67, 21.9, 21.7, 21.64, 21.61, 21.59, 21.53, 21.45, 21.4, 21.3, 19.2, 19.1.



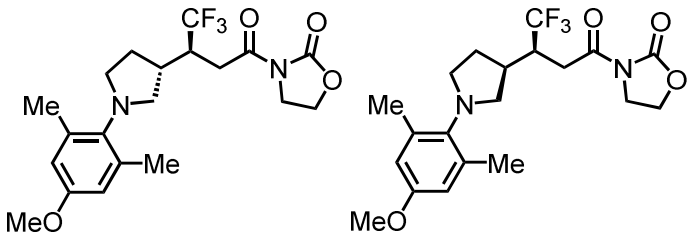
3.24b

(*S*)-3-((*R*)-3-((3*R*,5*R*)-1-Benzyl-5-(((*tert*-butyldimethylsilyl)oxy)diphenylmethyl) pyrrolidin-3-yl)-4,4,4-trifluorobutanoyl)-4-phenyloxazolidin-2-one (3.24b)

To a 15 mL oven-dried pressure vessel was added (*R*)-1-benzyl-2-(((*tert*-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine **3.19o** (0.10 mmol), (*S,E*)-4-phenyl-3-(4,4,4-trifluorobut-2-enoyl)oxazolidin-2-one **3.23b** (0.15 mmol), $B(C_6F_5)_3$ (10 mol%), ZnI_2 (10 mol%), HBpin (70 mol%) and benzene (0.60 mL) under a nitrogen atmosphere. The reaction mixture was allowed to heat for 36 hours at 70 °C. Upon completion, the reaction mixture was concentrated *in vacuo*. After purification by column chromatography (EtOAc:hexanes = 1:6), **3.24b** was obtained as a white solid (61 mg, 82%). The absolute configuration of **3.24b-(*R,R,R,S*)** was assigned based on X-ray crystallography data of **3.35b** (see **Sections 3.6.4**).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 6.6 Hz, 2H), 7.37 – 7.27 (m, 9H), 7.21 (t, *J* = 7.3 Hz, 4H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.04 (d, *J* = 7.4 Hz, 2H), 5.33 (dd, *J* = 8.8, 4.1 Hz, 1H), 4.65 (t, *J* = 8.8 Hz, 1H), 4.46 (br, 1H), 4.25 (dd, *J* = 9.0, 4.0 Hz, 1H), 4.02 (d, *J* = 9.8 Hz, 1H), 3.40 (d, *J* = 13.3 Hz, 1H), 3.02 (dd, *J* = 18.4, 6.2 Hz, 1H), 2.80 (dd, *J* = 18.4, 5.0 Hz, 1H), 2.63 (t, *J* = 7.8 Hz, 1H), 2.59 – 2.51 (m, 1H), 1.96 – 1.84 (m, 2H), 1.69 (q, *J* = 11.7 Hz, 1H), 1.33 – 1.18 (m, 1H), 0.87 (s, 9H), -0.44 (d, *J* = 17.4 Hz, 6H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 170.2, 153.6, 143.2, 140.3, 138.6, 130.2, 130.1, 130.1, 129.4, 129.0, 128.3, 128.2, 128.2, 127.7, 127.4, 127.2 (q, *J* = 266.8 Hz), 127.1, 126.6, 125.8, 70.2, 69.8, 61.7, 59.0, 58.1, 40.7 (q, *J* = 26.3 Hz), 35.4, 33.1, 29.9, 26.5, 19.1, -2.7, -2.9; **^{19}F NMR (376 MHz, $CDCl_3$):** δ -69.82 (d, *J* = 9.3 Hz); **IR (neat):** ν 2952, 2926, 2892, 2853, 1783, 1710, 1493, 1452, 1384, 1359, 1326, 1252, 1197, 1155,

1120, 1095, 1061, 854, 834, 774, 702 cm^{-1}; **HRMS (DART):** Calcd for $C_{43}H_{50}F_3N_2O_4Si$ (MH^+): 743.3486; found: 743.3486; **Specific Rotation:** $[\alpha]^{25}_D$ = -6.9° (c = 0.88, DCM).



3.24c-*anti* **3.24c-*syn***

3-((*S*)-4,4,4-Trifluoro-3-(1-(4-methoxy-2,6-dimethylphenyl)pyrrolidin-3-yl)butanoyl)oxazolidin-2-one (3.24c)

To a 15 mL oven-dried pressure vessel was added $Mg(ClO_4)_2$ (0.010 mmol, 10 mol%), **L5** (0.010 mmol, 10 mol%), Benzene (0.30 mL) under nitrogen atmosphere. The mixture was allowed to stir for 20 minutes at 22 °C. Subsequently, 1-(4-methoxy-2,6-dimethylphenyl)pyrrolidine **3.19s** (0.10 mmol), (*E*)-3-(4,4,4-trifluorobut-2-enoyl)oxazolidin-2-one **3.23c** (0.15 mmol), and benzene (0.30 mL) were added to the vial under nitrogen atmosphere, and the resulting mixture was allowed to stir at 22 °C for 12 h. Upon completion, the reaction mixture was concentrated *in vacuo*. ^{1}H NMR and ^{19}F NMR analyses of the unpurified product mixture using mesitylene and perfluorobenzene as the internal standard revealed that the diastereomeric ratio was 1.6:1. After purification by column chromatography (EtOAc:hexanes = 1:3), **3.24c** was obtained as a colorless liquid (28 mg, 67%). Further purification was carried out by PTLC using ethyl EtOAc:hexanes = 1:2 as the eluent to separate **3.24c-*anti*** and **3.24c-*syn***.

3.24c-*anti*. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.55 (s, 2H), 4.41 (t, *J* = 7.9 Hz, 2H), 4.09 – 3.93 (m, 2H), 3.73 (s, 3H), 3.41 (dd, *J* = 18.5, 7.2 Hz, 1H), 3.28 (q, *J* = 8.7 Hz, 1H), 3.22 – 3.09 (m, 3H), 3.08 – 2.92 (m, 2H), 2.65 (h, *J* = 8.3 Hz, 1H), 2.36 – 2.12 (m, 7H), 1.85 (p, *J* = 10.3 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.6, 157.0, 153.6, 139.8, 137.5, 127.8 (q, *J* = 280.5 Hz), 113.7, 62.3, 55.3, 53.9, 50.4, 42.8, 41.4 (q, *J* = 25.7 Hz), 39.0, 33.1, 33.0, 31.6, 19.0; **^{19}F NMR (376 MHz,**

$CDCl_3$): δ -69.12 (d, *J* = 9.3 Hz); **IR (neat):** ν 2921, 2837, 1778, 1701, 1601, 1480, 1387, 1363, 1319, 1280, 1222, 1194, 1124, 1067, 1040, 956, 856, 709, 671, 626 cm^{-1}; **HRMS (DART):** Calcd for $C_{20}H_{26}F_3N_2O_4$ (MH^+): 415.1839; found: 415.1819; **HPLC** (CHIRACPAK IA-3; 5%/ 95% isopropanol/ hexanes, 0.5 mL/min; tr = 25.7 min (minor), 36.0 min (major); 90:10 er); **Specific Rotation:** $[\alpha]^{25}_D$ = -6.0° (c = 1.0, DCM).

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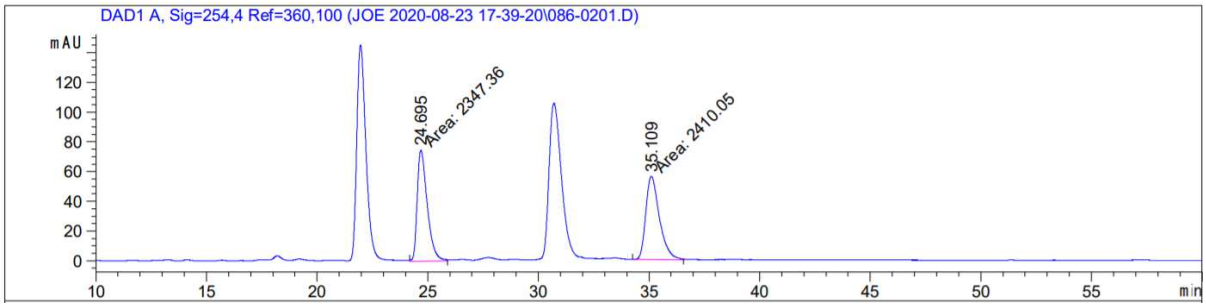

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2	35.109	MM	0.7172	2410.04810	56.00684	50.6588
Totals :				4757.41040	130.64258	

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Acq. Instrument : Wasa_LC1 Location : 87
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Inj Volume : 4.000 µl
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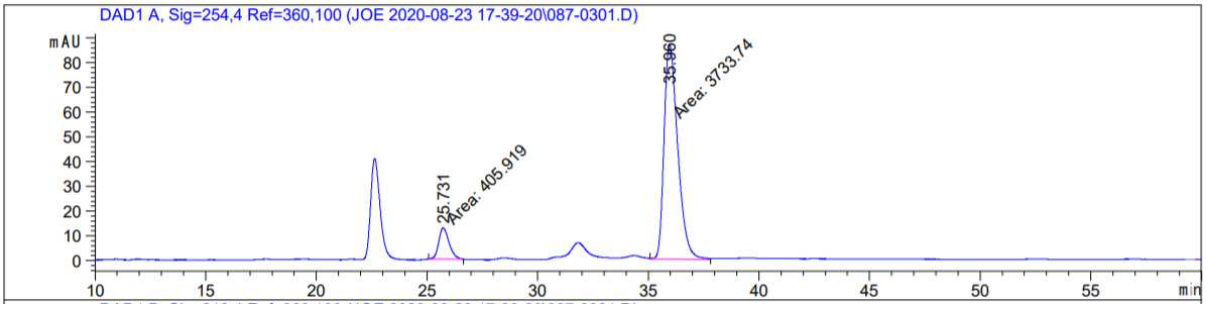
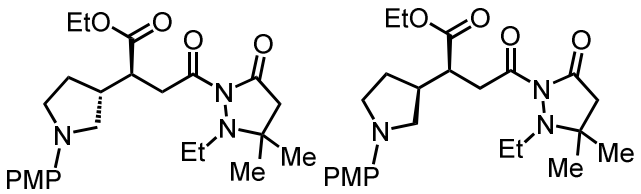
Method Info : Column6 60min-5.0% iPrOH 95% hexane-0.5mL



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.731	MM	0.5377	405.91949	12.58177	9.8056
2	35.960	MM	0.7167	3733.73560	86.82920	90.1944
Totals :				4139.65509	99.41098	

3.24c-*syn*. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.55 (s, 2H), 4.44 (t, *J* = 8.1 Hz, 2H), 4.09 – 4.00 (m, 2H), 3.73 (s, 3H), 3.45 – 3.34 (m, 1H), 3.32 – 3.19 (m, 2H), 3.19 – 3.10 (m, 3H), 3.07 (t, *J* = 8.8 Hz, 1H), 2.62 (dq, *J* = 16.7, 7.9 Hz, 1H), 2.21 (s, 6H), 2.10 – 2.01 (m, 1H), 1.79 (p, *J* = 10.2 Hz, 1H); **^{19}F NMR (470 MHz, $CDCl_3$):** δ -69.62 (d, *J* = 9.2 Hz); **IR (neat):** ν 2920, 2852, 1780, 1701, 1660, 1602, 1480, 1466, 1388, 1364, 1318, 1261, 1223, 1194, 1157, 1126, 1066, 1039 cm^{-1}; **HRMS (DART):** Calcd for $C_{20}H_{26}F_3N_2O_4$ (MH^+): 415.1839; found: 415.1837. **HPLC** (CHIRACPAK IA-3; 5%/ 95% isopropanol/ hexanes, 0.5 mL/min; tr = 22.0 min (major), 30.7 min (minor); 84:16 er); **Specific Rotation $[\alpha]^{25}_D$** = -5.3° (c = 0.15, DCM).



3.26a-(*R,S*) **3.26a-(*S,S*)**

Ethyl (*S*)-4-(2-ethyl-3,3-dimethyl-5-oxopyrazolidin-1-yl)-2-(1-(4-methoxyphenyl) pyrrolidin-3-yl)-4-oxobutanoate (3.26a)

1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidine **3.19t** was reacted with ethyl (*E*)-4-(2-ethyl-3,3-dimethyl-5-oxopyrazolidin-1-yl)-4-oxobut-2-enoate **3.25a** following the **General Procedure E** for 1 hour using $B(C_6F_5)_3$ (10 mol%), $Sc(OTf)_3$ (5.0 mol%), **L12** (6.0 mol%) and DCM as the solvent. ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that the diastereomeric ratio was 2.0:1. After purification by column chromatography (EtOAc:hexanes = 1:2), **3.26a** was obtained as a colorless liquid (36 mg, 80%). Further purification was carried out by PTLC using ethyl EtOAc:hexanes = 1:2 as the eluent to separate **3.26a-(*R,S*)** and **3.26a-(*S,S*)**. The absolute configuration for this product was assigned in analogy to that determined for product **3.26d** (see **Section 3.6.4**).

3.26a-(*R,S*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.84 (d, *J* = 9.0 Hz, 2H), 6.51 (d, *J* = 9.0 Hz, 2H), 4.22 – 4.08 (m, 2H), 3.75 (s, 3H), 3.46 – 3.37 (m, 2H), 3.33 (td, *J* = 8.7, 2.7 Hz, 1H), 3.29 – 3.21 (m, 1H), 3.05 (t, *J* = 8.7 Hz, 1H), 3.03 – 2.93 (m, 4H), 2.59 (s, 2H), 2.51 (q, *J* = 8.4 Hz, 1H), 2.14 – 2.05 (m, 1H), 1.90 (dq, *J* = 12.2, 8.9 Hz, 1H), 1.31 (d, *J* = 5.1 Hz, 6H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.07 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 175.5, 174.3, 169.6, 151.1, 142.8, 115.2, 112.6, 60.88, 60.85, 56.1, 52.3, 48.1, 47.3, 44.3, 43.9, 40.9, 37.9, 29.7, 26.1, 25.8, 14.4, 12.9; **IR (neat):** ν 2968, 2929, 2829, 1727, 1514, 1485, 1465, 1370, 1302, 1238, 1176, 1128, 1095, 1038, 812 cm^{-1}; **HRMS (DART):** Calcd for $C_{24}H_{36}N_3O_5$ (MH^+): 446.2650; found: 446.2656; **HPLC**

(CHIRACPAK IA-3; 10%/ 90% isopropanol/ hexanes, 1.0 mL/min; tr = 15.6 min (minor), 21.7 min (major); 97:3 er); **Specific Rotation $[\alpha]^{25}_{D}$** = -10.5° (c = 0.33, DCM).

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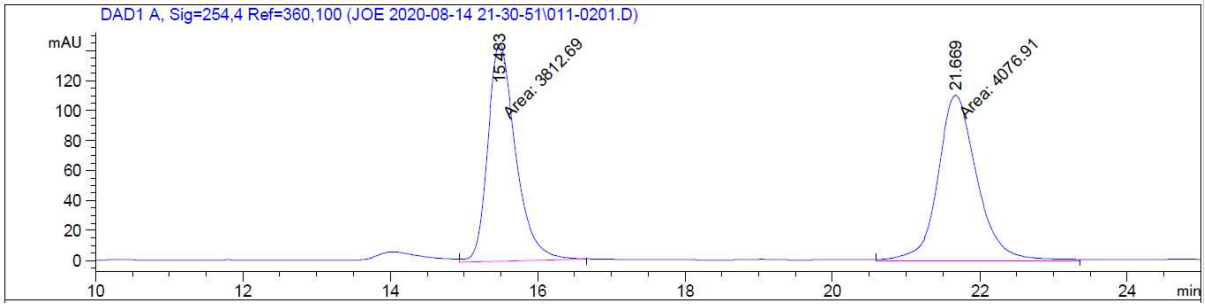

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

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Totals :				7889.59912	255.47435	

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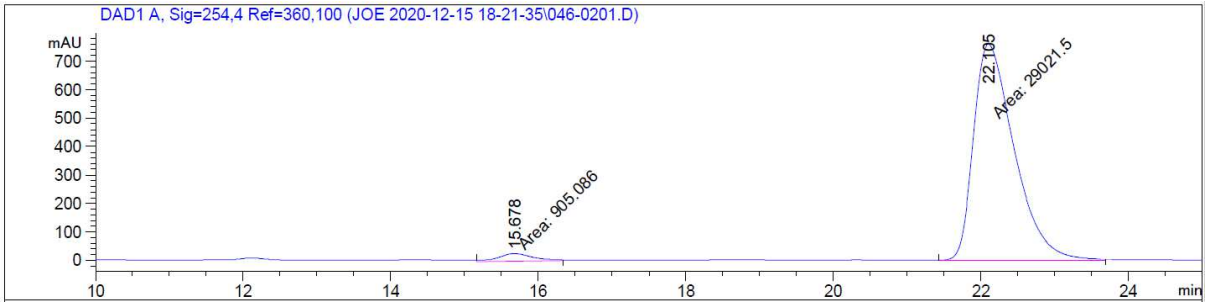

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.678	MM	0.5507	905.08649	27.39032	3.0244
2	22.105	MM	0.6368	2.90215e4	759.58032	96.9756
Totals :				2.99265e4	786.97065	

3.26a-(*S,S*). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.82 (d, *J* = 8.9 Hz, 2H), 6.49 (d, *J* = 9.0 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.74 (s, 3H), 3.44 – 3.29 (m, 3H), 3.28 – 3.20 (m, 1H), 3.12 (t, *J* = 8.8 Hz, 1H), 3.03 (dd, *J* = 18.0, 3.7 Hz, 1H), 3.02 – 2.90 (m, 3H), 2.58 (s, 2H), 2.56 – 2.48 (m, 1H), 2.18 (ddd, *J* = 12.6, 7.7, 5.3 Hz, 1H), 1.83 – 1.71 (m, 1H), 1.30 (d, *J* = 3.7 Hz, 6H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H); **IR (neat):** ν 2969, 2924, 2849, 1727, 1513, 1485, 1464, 1371, 1302, 1238, 1177, 1127, 1095, 1034, 813 cm^{-1}; **HRMS (DART):** Calcd for $C_{24}H_{36}N_3O_5$ (MH^+): 446.2650; found: 446.2643; **HPLC** (CHIRACPAK IA-3; 10%/ 90% isopropanol/ hexanes, 1.0 mL/min; tr = 29.0 min (major), 38.5 min (minor); 98:2 er); **Specific Rotation $[\alpha]^{25}_D$** = -2.0° (c = 0.10, DCM).

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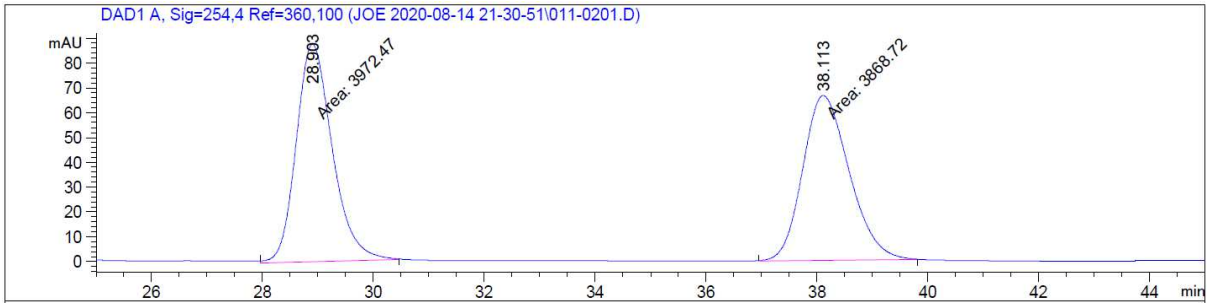

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

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2	38.113	MM	0.9717	3868.71851	66.35892	49.3384
Totals :				7841.18726	153.90034	

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                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2020-08-14 21-30-51\column6 10% IPA 90% hex 45min-1.
                  0ml.M
Last changed    : 8/14/2020 9:30:57 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2020-08-14 21-30-51\column6 10% IPA 90% hex 45min-1.
                  0ml.M (Sequence Method)
Last changed    : 12/18/2020 6:40:33 PM by SYSTEM
                  (modified after loading)
Method Info     : Column 6 10% IPA/90% hexane 1.0 mL/min 45 min
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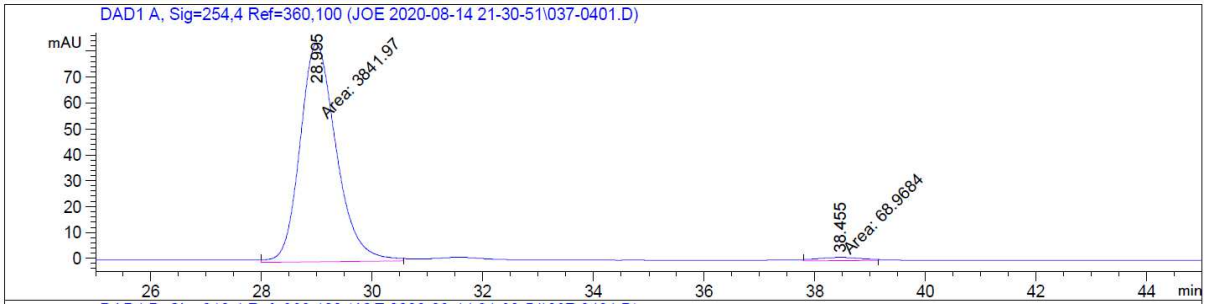
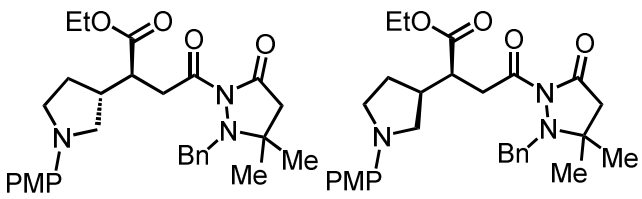


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.995	MM	0.7602	3841.96606	84.22824	98.2365
2	38.455	MM	0.9488	68.96841	1.21147	1.7635
Totals :				3910.93448	85.43971	



3.26b-(*R,S*) **3.26b-(*S,S*)**

Ethyl (*S*)-4-(2-benzyl-3,3-dimethyl-5-oxopyrazolidin-1-yl)-2-(1-(4-methoxyphenyl) pyrrolidin-3-yl)-4-oxobutanoate (3.26b)

1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidine **3.19t** was reacted with ethyl (*E*)-4-(2-benzyl-3,3-dimethyl-5-oxopyrazolidin-1-yl)-4-oxobut-2-enoate **3.25b** following the **General Procedure E** for 1 hour using $B(C_6F_5)_3$ (10 mol%), $Sc(OTf)_3$ (10 mol%), **L9** (12 mol%) and DCM as the solvent. ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that the diastereomeric ratio was 3.0:1. After purification by column chromatography (ether:hexanes = 3:2), **3.26b** was obtained as a colorless liquid (42 mg, 83%). Further purification was carried out by PTLC using ethyl ether:hexanes = 3:2 as the eluent to obtain **3.26b-(*R,S*)**. The absolute configuration for this product was assigned in analogy to that determined for product **3.26d** (see **Section 3.6.4**).

3.26b-(*R,S*). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39 (d, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.26 (d, *J* = 7.3 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.49 (d, *J* = 8.8 Hz, 2H), 4.11 (qd, *J* = 7.2, 2.0 Hz, 2H), 4.06 (d, *J* = 13.6 Hz, 1H), 3.99 (d, *J* = 13.9 Hz, 1H), 3.75 (s, 3H), 3.38 – 3.26 (m, 2H), 3.21 (td, *J* = 8.7, 6.5 Hz, 2H), 2.91 (t, *J* = 7.0 Hz, 1H), 2.79 (t, *J* = 10.0 Hz, 1H), 2.70 – 2.47 (m, 3H), 2.42 (q, *J* = 8.4 Hz, 1H), 2.06 – 2.01 (m, 1H), 1.81 (p, *J* = 9.5 Hz, 1H), 1.27 (d, *J* = 6.5 Hz, 6H), 1.21 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 174.6, 174.2, 169.1, 151.1, 142.8, 137.3, 129.6, 128.6, 127.8, 115.2, 112.6, 61.4, 60.8, 57.0, 56.1, 52.3, 48.1, 44.0, 43.6, 40.8, 37.5, 29.8, 29.7, 26.5, 26.0, 14.4; **IR (neat):** ν 2924, 2851, 1771, 1728, 1702, 1513, 1370, 1301, 1238,

1176, 1125, 1038, 812 cm^{-1}; **HRMS (DART):** Calcd for $C_{29}H_{38}N_3O_5$ (MH^+): 508.2806; found: 508.2805; **HPLC** (CHIRACPAK IA-3; 5%/ 95% isopropanol/ hexanes, 0.45 mL/min; tr = 82.9 min (major), 91.3 min (minor); 95:5 er); **Specific Rotation** $[\alpha]^{25}_D$ = -3.0° (c = 0.20, DCM).

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                                                Inj Volume : 4.000 µl
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                  0.45mL.M
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Method Info     : Column6 240min-5.0% iPrOH 95% hexane-0.45mL
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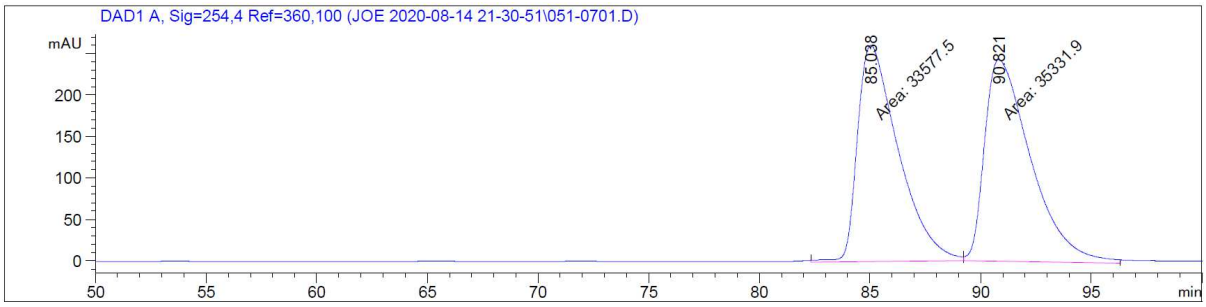

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	85.038	MM	2.1427	3.35775e4	261.18115	48.7270
2	90.821	MM	2.4172	3.53319e4	243.61862	51.2730
Totals :				6.89095e4	504.79977	

```
Acq. Operator   : SYSTEM                          Seq. Line :   9
Acq. Instrument : Wasa_LC1                         Location :   14
Injection Date  : 8/15/2020 9:59:52 AM                 Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2020-08-14 21-30-51\column6 5.0%IPA 95% hexane 240min-
                  0.45mL.M
Last changed    : 8/14/2020 9:30:57 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2020-08-14 21-30-51\column6 5.0%IPA 95% hexane 240min-
                  0.45mL.M (Sequence Method)
Last changed    : 12/18/2020 6:47:49 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 240min-5.0% iPrOH 95% hexane-0.45mL
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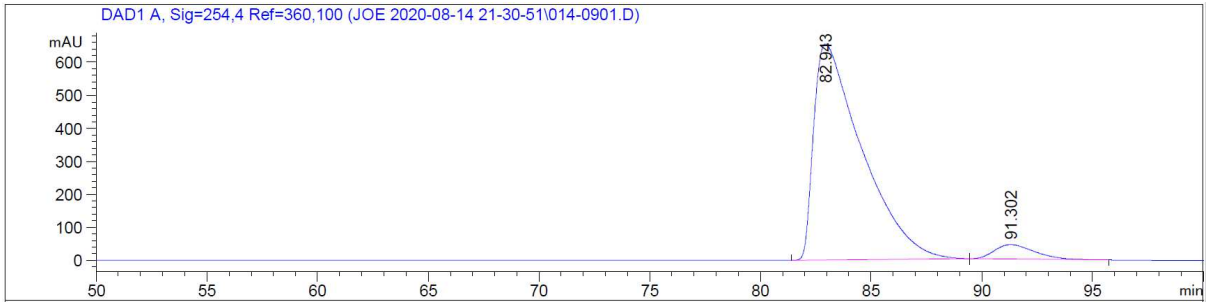

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	82.943	BB	2.1274	9.92032e4	655.57562	94.7781
2	91.302	BB	1.8391	5465.65527	43.52220	5.2219
Totals :				1.04669e5	699.09782	

3.26b ((*R*,*S*):(*S*,*S*)= 2.3:1). **^{1}H NMR (600 MHz, $CDCl_3$, *peaks from diastereomers are merged*):** δ 7.40 (dd, *J* = 7.4, 2.3 Hz, 2H), 7.35 – 7.29 (m, 2H), 7.29 – 7.23 (m, 1H), 6.89 – 6.79 (m, 2H), 6.55 – 6.44 (m, 2H), 4.20 – 4.09 (m, 2H), 4.09 – 4.03 (m, 1H), 4.03 – 3.95 (m, 1H), 3.83 – 3.70 (m, 3H), 3.39 – 3.27 (m, 2H), 3.27 – 3.14 (m, 2H), 3.09 – 2.87 (m, 1H), 2.87 – 2.75 (m, 1H), 2.74 – 2.36 (m, 4H), 2.13 – 1.98 (m, 1H), 1.86 – 1.63 (m, 1H), 1.31 – 1.25 (m, 6H), 1.25 – 1.19 (m, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 174.51, 174.47, 174.1, 173.9, 169.0 (*overlapped*), 151.01, 151.00, 142.8, 142.7, 137.3, 137.2, 129.5, 129.4, 128.51, 128.48, 127.7, 127.6, 115.0 (*overlapped*), 112.5 (*overlapped*), 61.3, 61.2, 60.72, 60.70, 56.84, 56.80, 56.00, 55.99, 52.15, 52.13, 48.0, 47.9, 44.0, 43.9, 43.5, 43.4, 40.6, 40.4, 37.4, 37.0, 29.8, 29.6, 26.4 (*overlapped*), 25.9 (*overlapped*), 14.30, 14.26; **HPLC** (CHIRACPAK IA-3; 5%/ 95% isopropanol/ hexanes, 0.45 mL/min; tr = 107.5 min (major), 191.0 min (minor); 95:5 er).

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                                                 Inj Volume : 4.000 µl
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                  0.45mL.M
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Analysis Method : C:\Chem32\1\Data\JOE 2020-08-14 21-30-51\column6 5.0%IPA 95% hexane 240min-
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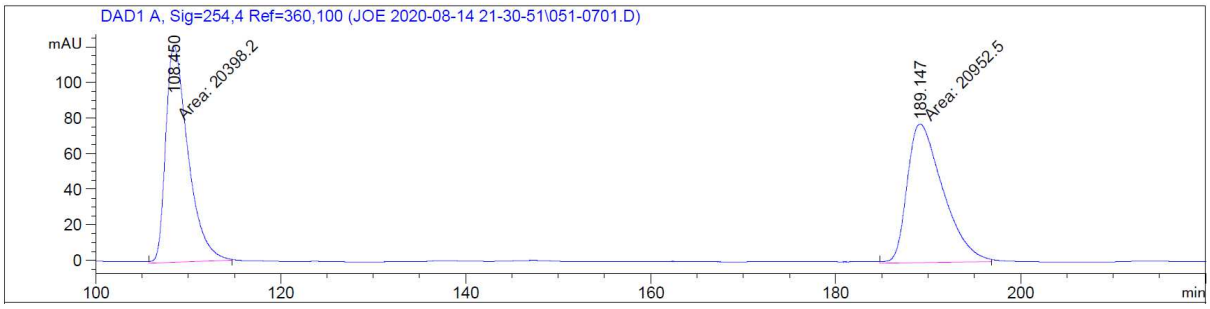

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

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1	108.450	MM	2.7896	2.03982e4	121.87206	49.3298
2	189.147	MM	4.4886	2.09525e4	77.79833	50.6702
Totals :				4.13507e4	199.67039	

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Injection Date  : 8/15/2020 9:59:52 AM                Inj :   1
                                                 Inj Volume : 4.000 µl
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                  0.45mL.M
Last changed    : 8/14/2020 9:30:57 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2020-08-14 21-30-51\column6 5.0%IPA 95% hexane 240min-
                  0.45mL.M (Sequence Method)
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Method Info     : Column6 240min-5.0% iPrOH 95% hexane-0.45mL
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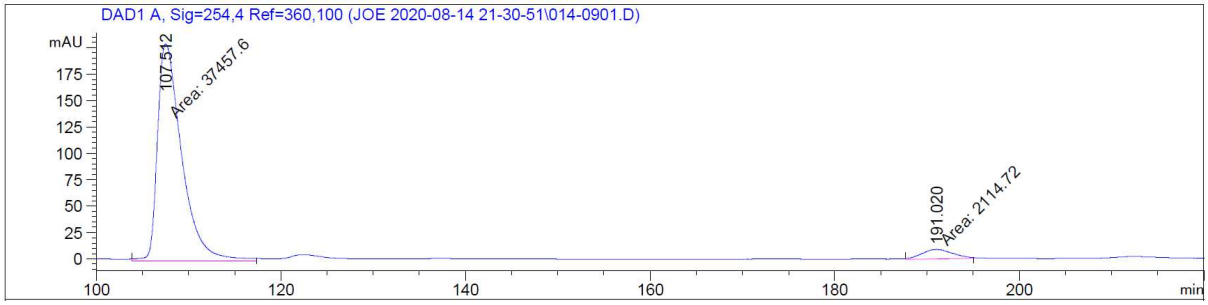
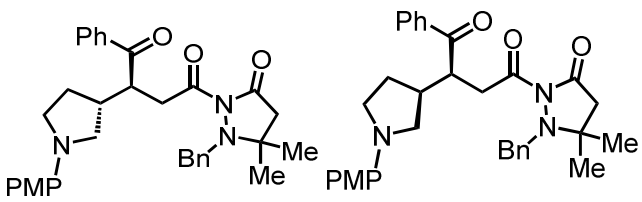


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	107.512	MM	3.0369	3.74576e4	205.56982	94.6561
2	191.020	MM	3.9514	2114.71851	8.91960	5.3439
Totals :				3.95723e4	214.48942	



3.26c-(*R,S*) **3.26c-(*S,S*)**

(*S*)-4-(2-Benzyl-3,3-Dimethyl-5-oxopyrazolidin-1-yl)-2-(1-(4-methoxyphenyl) pyrrolidin-3-yl)-1-phenylbutane-1,4-dione (3.26c)

1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidine **3.19t** was reacted with (*E*)-1-(2-benzyl-3,3-dimethyl-5-oxopyrazolidin-1-yl)-4-phenylbut-2-ene-1,4-dione **3.25c** following the **General Procedure E** for 12 hours using $B(C_6F_5)_3$ (10 mol%), $Sc(OTf)_3$ (10 mol%), **L9** (12 mol%) and DCM as the solvent. ^{1}H NMR analysis of the unpurified product mixture using mesitylene as the internal standard revealed that the diastereomeric ratio was 3.5:1. After purification by column chromatography (ethyl ether:hexanes = 3:2), **3.26c** was obtained as a colorless liquid (42 mg, 78%). Further purification was carried out by PTLC using ethyl ether:hexanes = 3:2 as the eluent to separate **3.26c-(*R,S*)** and **3.26c-(*S,S*)**. The absolute configuration for this product was assigned in analogy to that determined for product **3.26d** (see **Section 3.6.4**).

3.26c-(*R,S*). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.97 (d, *J* = 7.7 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.29 – 7.22 (m, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.45 (d, *J* = 8.7 Hz, 2H), 4.04 (d, *J* = 13.3 Hz, 1H), 3.94 (d, *J* = 13.6 Hz, 1H), 3.91 – 3.82 (m, 1H), 3.75 (s, 3H), 3.57 – 3.40 (m, 1H), 3.32 – 3.23 (m, 1H), 3.20 (td, *J* = 8.6, 2.3 Hz, 1H), 3.11 (q, *J* = 8.6 Hz, 1H), 2.97 – 2.87 (m, 1H), 2.59 (d, *J* = 17.1 Hz, 1H), 2.49 (d, *J* = 17.2 Hz, 1H), 2.47 – 2.37 (m, 1H), 1.86 – 1.77 (m, 1H), 1.62 – 1.53 (m, 2H), 1.31 – 1.23 (m, 7H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 203.3, 174.6, 169.7, 151.1, 142.7, 138.1, 137.1, 133.0, 129.8, 128.8, 128.63, 128.60, 127.8, 115.1, 112.5, 61.5, 57.1, 56.1, 52.2, 48.1, 44.3, 43.4, 41.4, 38.0, 30.1,

26.7, 25.8; **IR** (neat) ν 2924, 2850, 1742,1674, 1511, 1464, 1446, 1359, 1300, 1234, 1178, 1001, 957, 811, 729, 700, 595, 564 cm^{-1}; **HRMS (DART):** Calcd for $C_{33}H_{38}N_3O_4$ (MH^+): 540.2857; found: 540.2856; **HPLC** (CHIRACPAK IA-3; 10%/ 90% isopropanol/ hexanes, 1.0 mL/min; tr = 23.8 min (minor), 28.5 min (major); 95:5 er); **Specific Rotation** $[\alpha]^{25}_D$ = +35.0° (c = 0.40, DCM).

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                                                 Inj Volume : 4.000 µl
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                  0ml.M
Last changed    : 8/19/2020 8:35:37 PM by SYSTEM
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                  (modified after loading)
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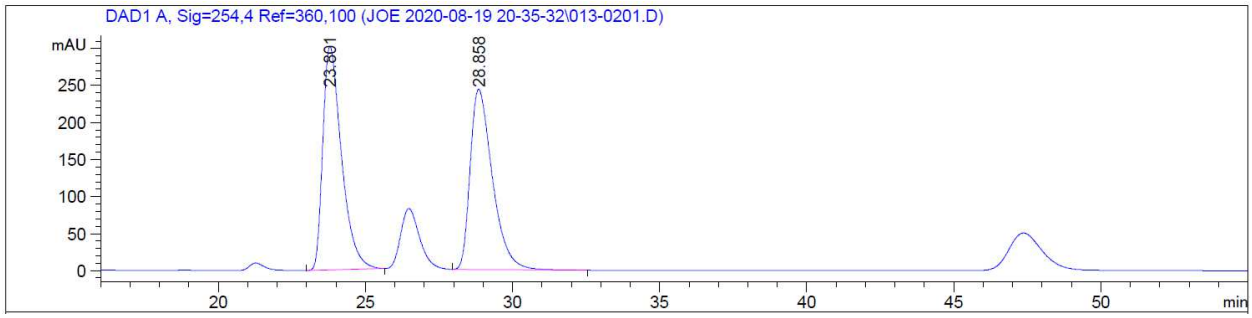

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.801	BB	0.6694	1.33297e4	301.72205	51.0074
2	28.858	BB	0.8069	1.28032e4	243.70734	48.9926
Totals :				2.61330e4	545.42938	

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Acq. Operator   : SYSTEM                          Seq. Line :   5
Acq. Instrument : Wasa_LC1                         Location :   44
Injection Date  : 12/11/2020 9:00:47 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2020-12-11 17-49-52\column6 10% IPA 90% hex 55min-1.
                  0ml.M
Last changed    : 12/11/2020 5:49:59 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2020-12-11 17-49-52\column6 10% IPA 90% hex 55min-1.
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                  (modified after loading)
Method Info     : Column 6 10% IPA/90% hexane 1.0 mL/min 55 min
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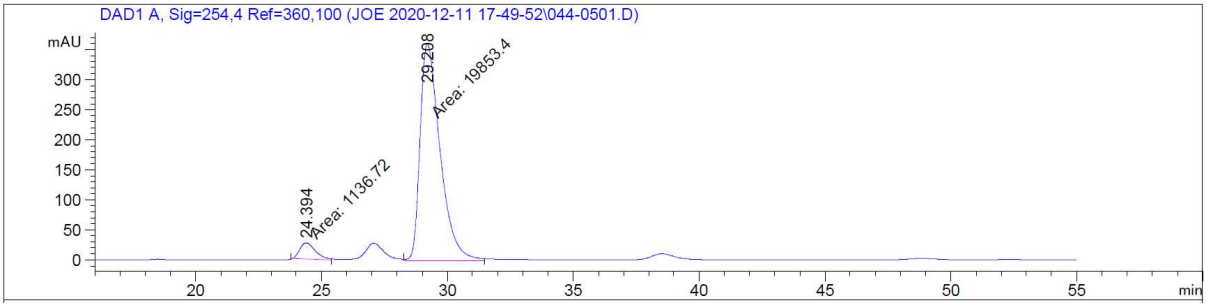

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.394	MM	0.7122	1136.71631	26.60268	5.4155
2	29.208	MM	0.9164	1.98534e4	361.08331	94.5845
Totals :				2.09901e4	387.68599	

3.26c-(*S*,*S*). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.96 (d, *J* = 6.7 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.34 (d, *J* = 7.1 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 2H), 7.22 (t, *J* = 7.1 Hz, 1H), 6.77 (d, *J* = 9.0 Hz, 2H), 6.35 (d, *J* = 9.0 Hz, 2H), 4.02 (d, *J* = 13.4 Hz, 1H), 3.99 – 3.90 (m, 2H), 3.72 (s, 3H), 3.53 – 3.38 (m, 1H), 3.27 (td, *J* = 8.7, 2.8 Hz, 1H), 3.17 (q, *J* = 8.8 Hz, 1H), 3.13 (t, *J* = 8.3 Hz, 1H), 2.83 (t, *J* = 8.6 Hz, 1H), 2.57 (d, *J* = 17.0 Hz, 1H), 2.54 – 2.45 (m, 2H), 2.08 – 1.99 (m, 1H), 1.75 – 1.62 (m, 1H), 1.31 – 1.23 (m, 7H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 202.9, 182.3, 174.6, 151.1, 142.7, 137.6, 137.1, 133.1, 129.7, 128.75, 128.67, 128.6, 127.8, 115.1, 112.6, 61.4, 57.0, 56.1, 52.2, 47.9, 44.3, 43.5, 41.1, 37.4, 29.5, 26.6, 25.9; **IR (neat):** ν 2922, 2850, 1744,1676, 1513, 1484, 1447, 1364, 1301, 1237, 1179, 1038, 812, 699 cm^{-1}; **HRMS (DART):** Calcd for $C_{33}H_{38}N_3O_4$ (MH^+): 540.2857; found: 540.2828; **HPLC** (CHIRACPAK IA-3; 10%/ 90% isopropanol/ hexanes, 1.0 mL/min; tr = 26.2 min (minor), 47.0 min (major); 95:5 er); **Specific Rotation $[\alpha]^{25}_D$** = +12.0° (c = 0.20, DCM).

```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                         Location :   13
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                                                  Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2020-08-19 20-35-32\column6 10% IPA 90% hex 55min-1.
                  0ml.M
Last changed    : 8/19/2020 8:35:37 PM by SYSTEM
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                  0ml.M (Sequence Method)
Last changed    : 8/21/2020 3:27:04 PM by SYSTEM
                  (modified after loading)
Method Info     : Column 6 10% IPA/90% hexane 1.0 mL/min 55 min
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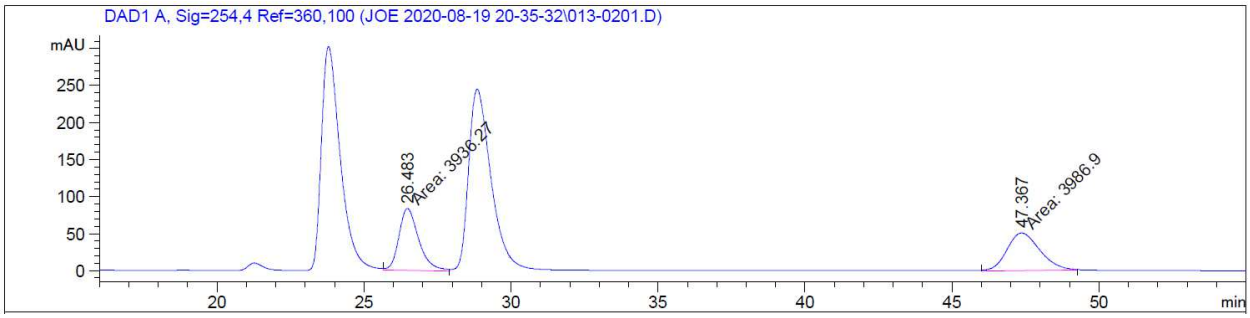

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.483	MM	0.7830	3936.26709	83.78169	49.6805
2	47.367	MM	1.3058	3986.90332	50.88859	50.3195
Totals :				7923.17041	134.67028	

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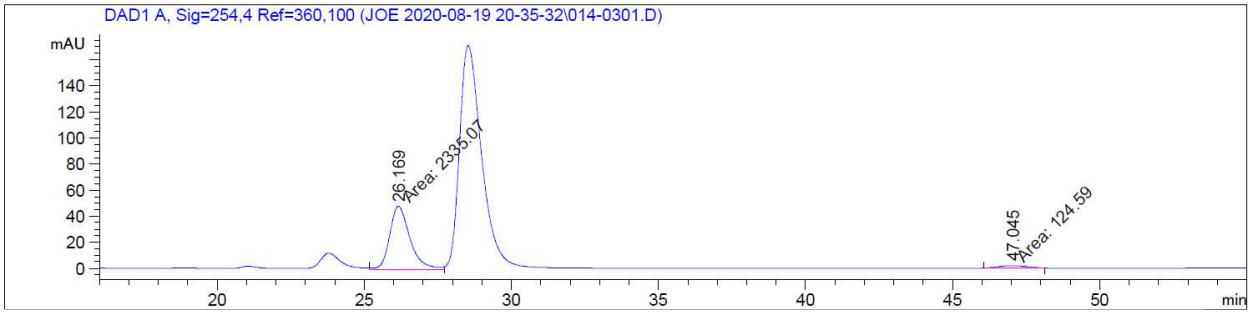
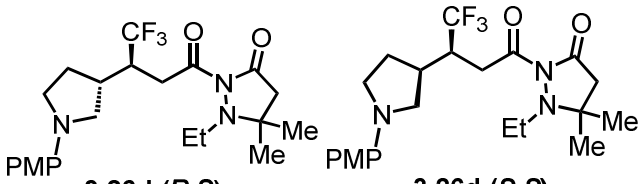
Acq. Operator   : SYSTEM                          Seq. Line :   3
Acq. Instrument : Wasa_LC1                         Location :   14
Injection Date  : 8/19/2020 10:28:47 PM               Inj :   1
                                                  Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2020-08-19 20-35-32\column6 10% IPA 90% hex 55min-1.
                  0ml.M
Last changed    : 8/19/2020 8:35:37 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2020-08-19 20-35-32\column6 10% IPA 90% hex 55min-1.
                  0ml.M (Sequence Method)
Last changed    : 8/21/2020 3:27:04 PM by SYSTEM
                  (modified after loading)
Method Info     : Column 6 10% IPA/90% hexane 1.0 mL/min 55 min
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.169	MM	0.8005	2335.06763	48.61831	94.9347
2	47.045	MM	1.0958	124.58971	1.89503	5.0653
Totals :				2459.65733	50.51335	



3.26d-(*R,S*) **3.26d-(*S,S*)**

1-Ethyl-5,5-dimethyl-2-((*S*)-4,4,4-trifluoro-3-(1-(4-methoxyphenyl)pyrrolidin-3-yl)butanoyl)pyrazolidin-3-one (3.26d)

1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidine **3.19t** was reacted with (*E*)-1-ethyl-5,5-dimethyl-2-(4,4,4-trifluorobut-2-enoyl)pyrazolidin-3-one **3.25d** following the **General Procedure E** for 3 hours using $B(C_6F_5)_3$ (10 mol%), $Sc(OTf)_3$ (10 mol%), **L12** (12 mol%) and DCM as the solvent. ^{1}H NMR and ^{19}F NMR analyses of the unpurified product mixture using mesitylene and perfluorobenzene as the internal standard revealed that the diastereomeric ratio was 6.7:1. After purification by column chromatography (EtOAc:hexanes = 1:2), **3.26d** was obtained as a colorless liquid (27 mg, 62%). Further purification was carried out by PTLC using EtOAc:hexanes = 1:2 as the eluent to separate **3.26d-(*R,S*)** and **3.26d-(*S,S*)**. The absolute configuration of product was assigned based on X-ray crystallography data of **3.29d** (see **SI-Sections 4** and **10**).

3.26d-(*R,S*). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 6.83 (d, *J* = 8.9 Hz, 2H), 6.50 (d, *J* = 9.0 Hz, 2H), 3.75 (s, 3H), 3.41 (dd, *J* = 18.3, 6.9 Hz, 1H), 3.38 – 3.32 (m, 2H), 3.31 – 3.22 (m, 2H), 3.09 (t, *J* = 9.1 Hz, 1H), 3.02 (qd, *J* = 6.9, 2.7 Hz, 2H), 2.89 (dd, *J* = 18.4, 4.3 Hz, 1H), 2.69 – 2.54 (m, 3H), 2.23 (dt, *J* = 13.0, 7.3 Hz, 1H), 1.83 (p, *J* = 10.3 Hz, 1H), 1.32 (s, 6H), 1.09 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 175.5, 168.4, 151.3, 142.6, 127.8 (q, *J* = 280.4 Hz), 115.1, 112.7, 60.8, 56.1, 51.3, 48.1, 47.2, 44.0, 40.9 (q, *J* = 26.0 Hz), 37.8, 33.2, 30.2, 26.1, 25.7, 12.9; **^{19}F NMR (470 MHz, $CDCl_3$):** δ -69.19 (d, *J* = 9.5 Hz); **IR (neat):** ν 2974, 2934, 2853, 2833, 1745, 1709, 1514, 1373, 1303, 1260, 1238, 1159, 1125, 1038, 813, 690 cm^{-1}; **HRMS (DART):** Calcd for $C_{22}H_{31}F_3N_3O_3$ (MH^+): 442.2312; found: 442.2305; **HPLC** (CHIRACPAK IA-3; 5%/ 95%

isopropanol/ hexanes, 1.0 mL/min; tr = 15.8 min (major), 31.5 min (minor); 96:4 er); **Specific Rotation $[\alpha]^{25}_{D}$** = -7.3° (c = 0.20, DCM).

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Acq. Operator   : SYSTEM                          Seq. Line :   4
Acq. Instrument : Wasa_LC1                         Location :   94
Injection Date  : 11/11/2020 11:10:16 PM               Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2020-11-11 21-05-19\column6 5%IPA 95% hexane 40min-1.
                  0mL.M
Last changed    : 11/11/2020 9:05:25 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2020-11-11 21-05-19\column6 5%IPA 95% hexane 40min-1.
                  0mL.M (Sequence Method)
Last changed    : 11/12/2020 7:05:24 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 40min-5% iPrOH 95% hexane-1.0mL
```
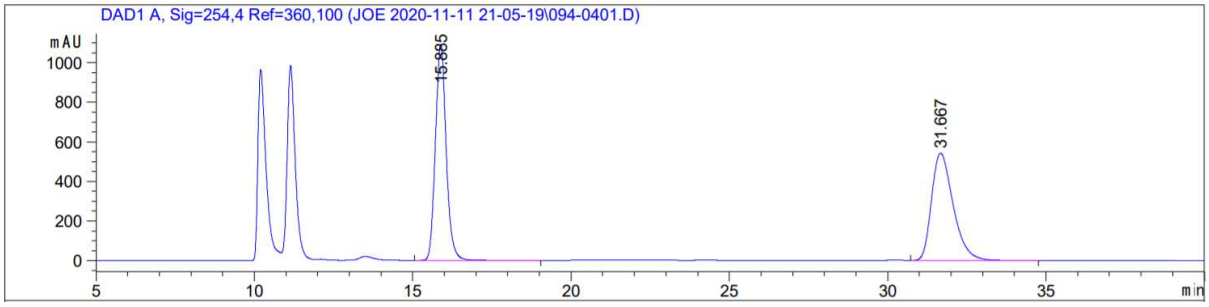
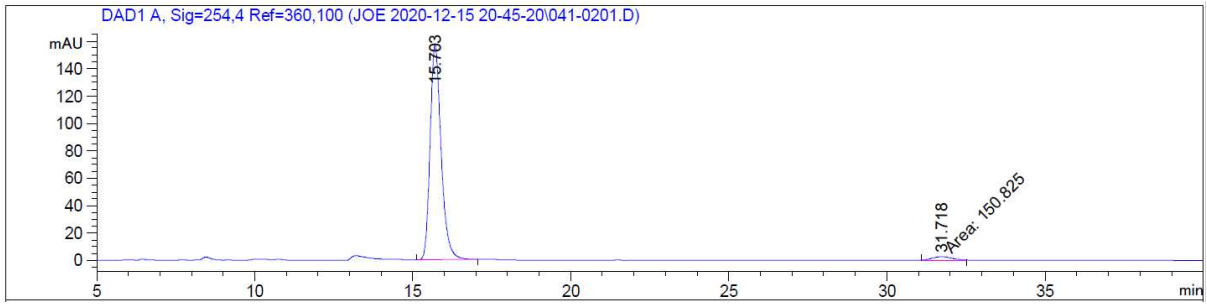



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.885	BB	0.3654	2.57801e4	1092.16479	50.1031
2	31.667	BB	0.7264	2.56739e4	542.24054	49.8969
Totals :				5.14540e4	1634.40533	

```
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                         Location :   41
Injection Date  : 12/15/2020 10:27:38 PM              Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2020-12-15 20-45-20\column6 5%IPA 95% hexane 40min-1.
                  0mL.M
Last changed    : 12/15/2020 8:45:26 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2020-12-15 20-45-20\column6 5%IPA 95% hexane 40min-1.
                  0mL.M (Sequence Method)
Last changed    : 12/16/2020 11:06:35 AM by SYSTEM
                  (modified after loading)
Method Info     : Column6 40min-5% iPrOH 95% hexane-1.0mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.703	BB	0.3699	3790.19409	156.84543	96.1729
2	31.718	MM	0.8379	150.82510	2.99991	3.8271
Totals :				3941.01920	159.84534	

3.26d ((*R,S*):(*S,S*)= 1:4.7). **^{1}H NMR (600 MHz, $CDCl_3$, *peaks from diastereomers are merged*):** δ 6.86 – 6.81 (m, 2H), 6.53 – 6.48 (m, 2H), 3.77 – 3.73 (m, 3H), 3.50 – 3.39 (m, 1H), 3.39 – 3.30 (m, 2H), 3.30 – 3.20 (m, 2H), 3.11 – 2.86 (m, 4H), 2.67 – 2.54 (m, 3H), 2.27 – 2.06 (m, 1H), 1.84 (p, *J* = 10.4 Hz, 1H), 1.33 – 1.28 (m, 6H), 1.11 – 1.05 (m, 3H); **^{19}F NMR (470 MHz, $CDCl_3$):** δ -69.18 (d, *J* = 9.6 Hz, **7f-(*S,S*)**), -69.48 (d, *J* = 9.2 Hz, **3.26d-(*R,S*)**); **HRMS** (DART) Calcd for $C_{22}H_{31}F_3N_3O_3$ (MH^+): 442.2312; found: 442.2305; **HPLC** (CHIRACPAK IA-3; 5%/ 95% isopropanol/ hexanes, 1.0 mL/min; tr = 10.2 min (major), 11.3 min (minor); 95:5 er).

```
Acq. Operator   : SYSTEM                          Seq. Line :   4
Acq. Instrument : Wasa_LC1                         Location :   94
Injection Date  : 11/11/2020 11:10:16 PM               Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2020-11-11 21-05-19\column6 5%IPA 95% hexane 40min-1.
                  0mL.M
Last changed    : 11/11/2020 9:05:25 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2020-11-11 21-05-19\column6 5%IPA 95% hexane 40min-1.
                  0mL.M (Sequence Method)
Last changed    : 11/12/2020 7:05:24 PM by SYSTEM
                  (modified after loading)
Method Info     : Column6 40min-5% iPrOH 95% hexane-1.0mL
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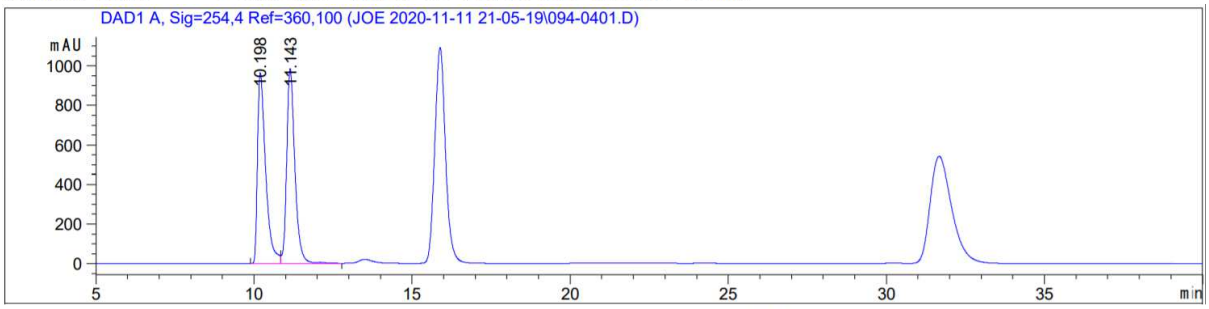


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Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.198 BV    0.2712 1.72915e4   964.19971  49.4346
   2  11.143 VV R  0.2701 1.76871e4   985.10260  50.5654

Totals :                  3.49786e4  1949.30231
```
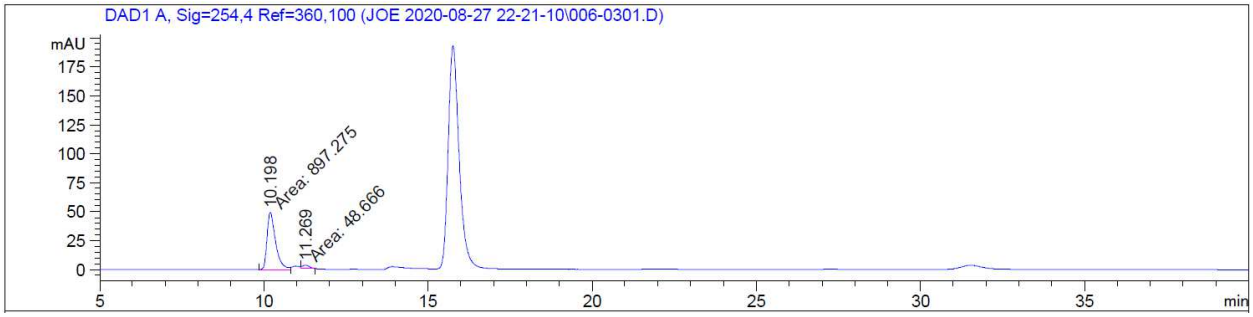
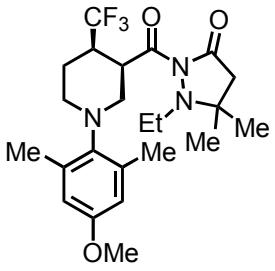

```
Acq. Operator   : SYSTEM                          Seq. Line :   3
Acq. Instrument : Wasa_LC1                         Location :   6
Injection Date  : 8/27/2020 11:44:28 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2020-08-27 22-21-10\column6 5%IPA 95% hexane 40min-1.
                  0mL.M
Last changed    : 8/27/2020 10:21:17 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2020-08-27 22-21-10\column6 5%IPA 95% hexane 40min-1.
                  0mL.M (Sequence Method)
Last changed    : 8/28/2020 10:27:11 AM by SYSTEM
                  (modified after loading)
Method Info     : Column6 40min-5% iPrOH 95% hexane-1.0mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.198	MM	0.3023	897.27521	49.46244	94.8553
2	11.269	MM	0.2722	48.66601	2.97946	5.1447
Totals :				945.94122	52.44190	



3.26e

1-Ethyl-2-((3*R*,4*R*)-1-(4-methoxy-2,6-dimethylphenyl)-4-(trifluoromethyl)piperidine-3-carbonyl)-5,5-dimethylpyrazolidin-3-one (3.26e)

N-Ethyl-4-methoxy-*N*,2,6-trimethylaniline **3.19e** was reacted with (*E*)-1-ethyl-5,5-dimethyl-2-(4,4,4-trifluorobut-2-enoyl)pyrazolidin-3-one **3.25d** following the **General Procedure E** for 24 hours using $B(C_6F_5)_3$ (10 mol%), $Sc(OTf)_3$ (20 mol%), **L12** (24 mol%) and DCM as the solvent. After purification by column chromatography (Et_3N:ethyl ether:hexanes = 1:50:50), **3.26e** was obtained as a single diastereomer and as colorless liquid (31 mg, 67%). The absolute configuration for this product was assigned in analogy to that determined for product **3.26d** (see **Section 3.6.4**).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.61 (d, *J* = 3.0 Hz, 1H), 6.46 (d, *J* = 3.0 Hz, 1H), 4.38 – 4.23 (m, 1H), 3.74 (s, 3H), 3.24 (td, *J* = 12.1, 2.6 Hz, 1H), 3.19 (d, *J* = 7.3 Hz, 2H), 3.07 (dq, *J* = 14.2, 7.2 Hz, 1H), 3.04 – 2.93 (m, 2H), 2.91 (dq, *J* = 13.8, 7.1 Hz, 1H), 2.62 (d, *J* = 17.3 Hz, 1H), 2.54 (d, *J* = 17.3 Hz, 1H), 2.37 (s, 3H), 2.25 (s, 3H), 1.98 (dd, *J* = 12.8, 4.3 Hz, 1H), 1.82 (qd, *J* = 12.4, 4.6 Hz, 1H), 1.29 (s, 6H), 1.03 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 175.3, 169.9, 157.0, 141.3, 139.5, 138.1, 127.5 (q, *J* = 280.2 Hz), 114.2, 113.5, 60.2, 55.4, 53.4, 48.9, 46.9, 44.4, 41.9, 41.1 (q, *J* = 26.0 Hz), 26.4, 25.3, 25.1, 20.0, 19.7, 12.7; **^{19}F NMR (376 MHz, $CDCl_3$):** δ -70.88 (d, *J* = 7.7 Hz); **IR (neat):** ν 2960, 2836, 1742,1701, 1601, 1485, 1467, 1443, 1388, 1373, 1303, 1227, 1191, 1151, 1130, 1085, 1034, 999, 855, 731, 619 cm^{-1}; **HRMS (DART):** Calcd for $C_{23}H_{32}F_3N_3O_3$ (MH^+): 456.2468; found: 456.2460; **HPLC** (CHIRACPAK IA-3; 5%/ 95%

isopropanol/ hexanes, 0.5 mL/min; tr = 12.5 min (minor), 16.0 min (major); 95:5 er); **Specific Rotation $[\alpha]^{25}_{D}$** = +7.0° (c = 0.40, DCM).

```
Acq. Operator   : SYSTEM                          Seq. Line :   2
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Injection Date  : 8/27/2020 12:10:12 PM               Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2020-08-27 11-37-07\column6 5%IPA 95% hexane 30min-0.
                  5mL.M
Last changed    : 8/27/2020 11:37:13 AM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2020-08-27 11-37-07\column6 5%IPA 95% hexane 30min-0.
                  5mL.M (Sequence Method)
Last changed    : 8/28/2020 10:32:40 AM by SYSTEM
                  (modified after loading)
Method Info     : Column6 30min-5.0% iPrOH 95% hexane-0.5mL
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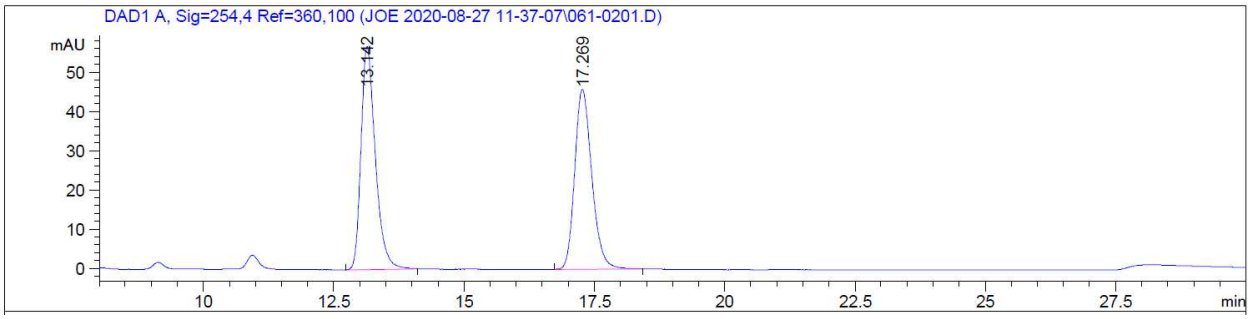
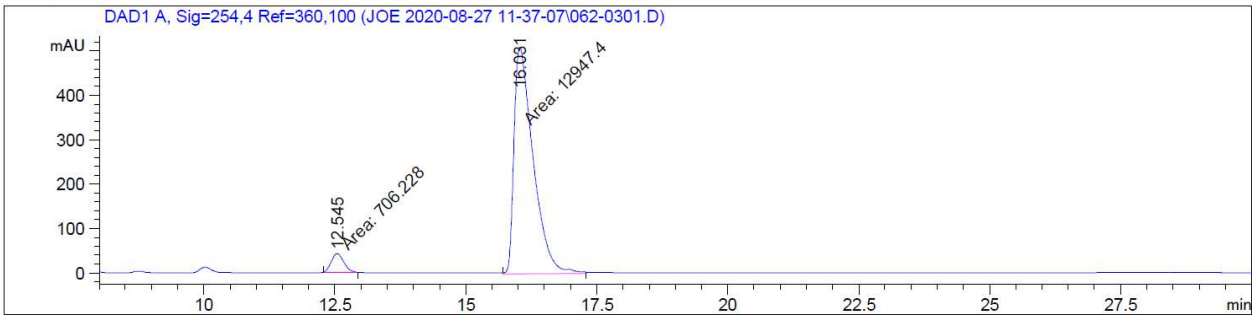


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

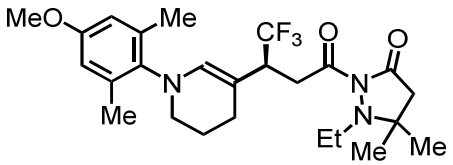
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.142	BB	0.2887	1084.45898	56.82304	50.9372
2	17.269	BB	0.3497	1044.55127	45.87325	49.0628
Totals :				2129.01025	102.69629	

```
Acq. Operator   : SYSTEM                          Seq. Line :   3
Acq. Instrument : Wasa_LC1                         Location :   62
Injection Date  : 8/27/2020 12:41:09 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2020-08-27 11-37-07\column6 5%IPA 95% hexane 30min-0.
                  5mL.M
Last changed    : 8/27/2020 11:37:13 AM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2020-08-27 11-37-07\column6 5%IPA 95% hexane 30min-0.
                  5mL.M (Sequence Method)
Last changed    : 8/28/2020 10:32:40 AM by SYSTEM
                  (modified after loading)
Method Info     : Column6 30min-5.0% iPrOH 95% hexane-0.5mL
```



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.545	MM	0.2768	706.22766	42.52583	5.1724
2	16.031	MM	0.4221	1.29474e4	511.25565	94.8276
Totals :				1.36537e4	553.78147	



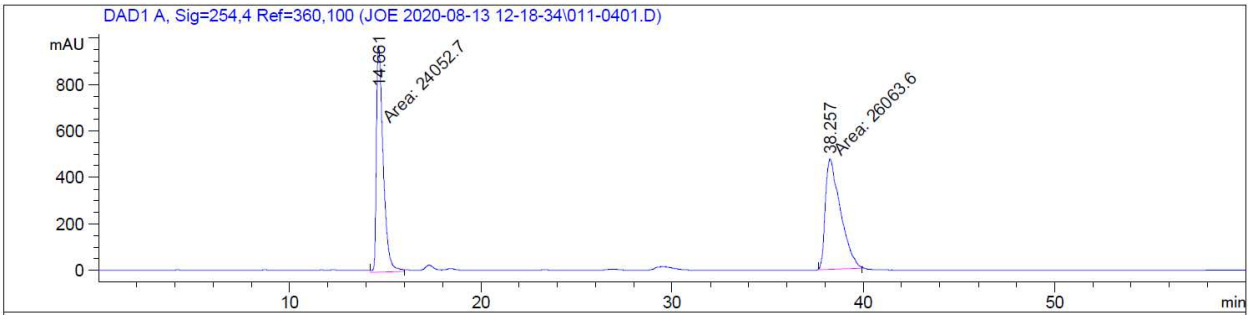
3.26f

(*S*)-1-Ethyl-5,5-dimethyl-2-(4,4,4-trifluoro-3-(1-(4-methoxy-2,6-dimethylphenyl)-1,4,5,6-tetrahydropyridin-3-yl)butanoyl)pyrazolidin-3-one (3.26f)

1-(4-Methoxy-2,6-dimethylphenyl)piperidine **3.19g** was reacted with (*E*)-1-ethyl-5,5-dimethyl-2-(4,4,4-trifluorobut-2-enoyl)pyrazolidin-3-one **3.25d** following the **General Procedure E** for 12 hours using $B(C_6F_5)_3$ (10 mol%), $Sc(OTf)_3$ (10 mol%), **L12** (12 mol%) and DCM as the solvent. After purification by column chromatography (ethyl ether:hexane = 1:1), **3.26f** was obtained as a colorless liquid (46 mg, 95%). The absolute configuration for this product was assigned in analogy to that determined for product **3.26d** (see **Section 3.6.4**).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.55 (s, 2H), 5.91 (s, 1H), 3.75 (s, 3H), 3.43 – 3.29 (m, 2H), 3.20 – 3.07 (m, 3H), 2.96 (q, *J* = 7.0 Hz, 2H), 2.57 (s, 2H), 2.29 – 2.10 (m, 8H), 2.05 – 1.83 (m, 2H), 1.29 (s, 6H), 1.06 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 175.3, 168.2, 157.5, 138.8, 138.38, 138.37, 135.6, 127.7 (q, *J* = 280.9 Hz), 113.53, 113.50, 95.9, 60.6, 55.4, 47.3, 47.2, 44.8 (q, *J* = 27.0 Hz), 44.0, 34.32, 34.30, 25.9, 25.8, 23.2, 22.7, 18.44, 18.41, 13.0; **^{19}F NMR (376 MHz, $CDCl_3$):** δ -70.18 (d, *J* = 9.3 Hz); **IR (neat):** ν 2925, 2840, 1743, 1708, 1654, 1602, 1487, 1467, 1442, 1374, 1319, 1301, 1274, 1152, 1099, 1068, 999, 857, 616 cm^{-1}; **HRMS (DART):** $C_{25}H_{35}F_3N_3O_3$ (MH^+): 482.2625; found: 482.2617; **HPLC** (CHIRACPAK IA-3; 2.5%/ 97.5% isopropanol/ hexanes, 0.5 mL/min; tr = 15.4 min (minor), 38.7 min (major); 95:5 er); **Specific Rotation $[\alpha]^{25}_D$** = +12.9° (c = 1.0, DCM).

Acq. Operator : SYSTEM Seq. Line : 4
Acq. Instrument : Wasa_LC1 Location : 11
Injection Date : 8/13/2020 2:42:49 PM Inj : 1
Inj Volume : 4.000 µl
Method : C:\Chem32\1\Data\JOE 2020-08-13 12-18-34\column6 2.5%IPA 97.5% hexane 60min -0.5mL.M (Sequence Method)
Last changed : 8/13/2020 12:18:40 PM by SYSTEM
Method Info : Column6 60min-2.5% iPrOH 99% hexane-0.5mL



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.661	MM	0.4109	2.40527e4	975.62061	47.9938
2	38.257	MM	0.9147	2.60636e4	474.88654	52.0062
Totals :				5.01163e4	1450.50714	

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Acq. Operator   : SYSTEM                          Seq. Line :   5
Acq. Instrument : Wasa_LC1                         Location :   12
Injection Date  : 8/13/2020 3:43:44 PM                Inj :   1
                                                Inj Volume : 4.000 µl
Method          : C:\Chem32\1\Data\JOE 2020-08-13 12-18-34\column6 2.5%IPA 97.5% hexane 60min
                  -0.5mL.M (Sequence Method)
Last changed    : 8/13/2020 12:18:40 PM by SYSTEM
Method Info     : Column6 60min-2.5% iPrOH 99% hexane-0.5mL
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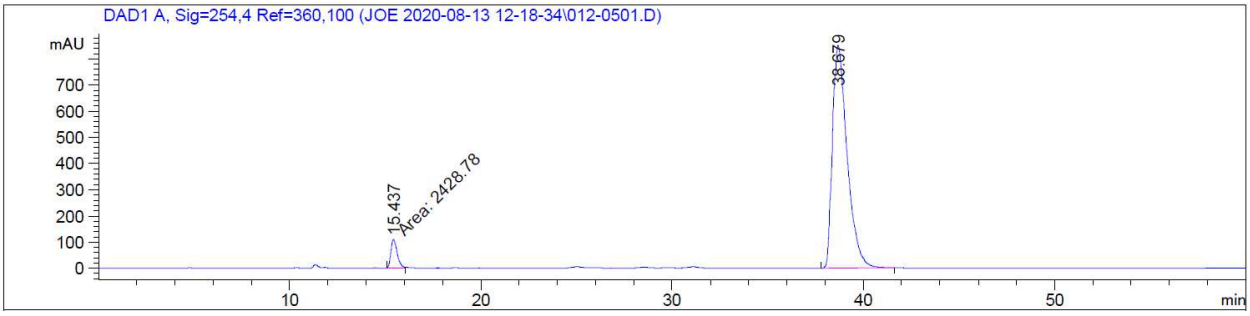
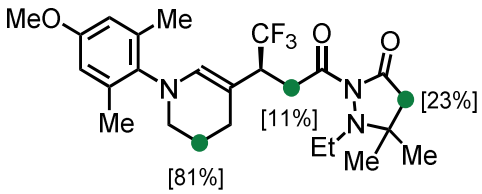


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.437	MM	0.3751	2428.77881	107.90679	5.0724
2	38.679	BB	0.7134	4.54539e4	850.64508	94.9276
Totals :				4.78826e4	958.55187	



3.26f-*d*

(*S*)-1-Ethyl-5,5-dimethyl-2-(4,4,4-trifluoro-3-(1-(4-methoxy-2,6-dimethylphenyl)-1,4,5,6-tetrahydropyridin-3-yl-5,5-d_2)butanoyl)pyrazolidin-3-one (3.26f-*d*)

1-(4-Methoxy-2,6-dimethylphenyl)piperidine-3,3,5,5-d_4 **3.19g-*d*** was reacted with (*E*)-1-ethyl-5,5-dimethyl-2-(4,4,4-trifluorobut-2-enoyl)pyrazolidin-3-one **3.25d** following the **General Procedure E** for 12 hours using $B(C_6F_5)_3$ (10 mol%), $Sc(OTf)_3$ (10 mol%), **L12** (12 mol%) and DCM as the solvent. After purification by column chromatography (ethyl ether:hexanes = 1:1), **3.26f-*d*** was obtained as a colorless liquid (41 mg, 84%). The absolute configuration for this product was assigned in analogy to that determined for product **3.26d**(see **Section 3.6.4**).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.55 (s, 2H), 5.91 (s, 1H), 3.75 (s, 3H), 3.42 – 3.30 (m, 1.78H, 11%D), 3.22 – 3.08 (m, 3H), 2.97 (q, *J* = 7.2 Hz, 2H), 2.60 – 2.50 (m, 1.53H, 23%D), 2.20 – 2.08 (m, 8H), 1.98 – 1.87 (m, 0.32H, 81%D), 1.29 (s, 6H), 1.06 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 175.3, 168.2, 157.5, 138.8, 138.41, 138.40, 135.6, 127.7 (q, *J* = 281.0 Hz), 113.55, 113.52, 96.0, 60.63, 60.56, 55.4, 47.3, 47.22, 47.20, 44.8 (q, *J* = 27.0 Hz), 44.0, 34.3, 25.9, 23.0, 18.5, 18.4, 13.0; **^{19}F NMR (564 MHz, $CDCl_3$):** δ -70.18 (d, *J* = 8.6 Hz); **IR (neat):** ν 2971, 2934, 2840, 1744, 1707, 1655, 1601, 1486, 1467, 1374, 1319, 1155, 1102, 856, 616 cm^{-1}; **HRMS** (DART) Calcd for $C_{25}H_{33}D_2F_3N_3O_3$ (MH^+): 484.5804; found: 484.2746; **HPLC** (CHIRACPAK IA-3; 2.5%/ 97.5% isopropanol/ hexanes, 0.5 mL/min; tr = 12.8 min (minor), 33.6 min (major); 95:5 er); **Specific Rotation $[\alpha]^{25}_D$** = +2.1° (c = 0.53, DCM).

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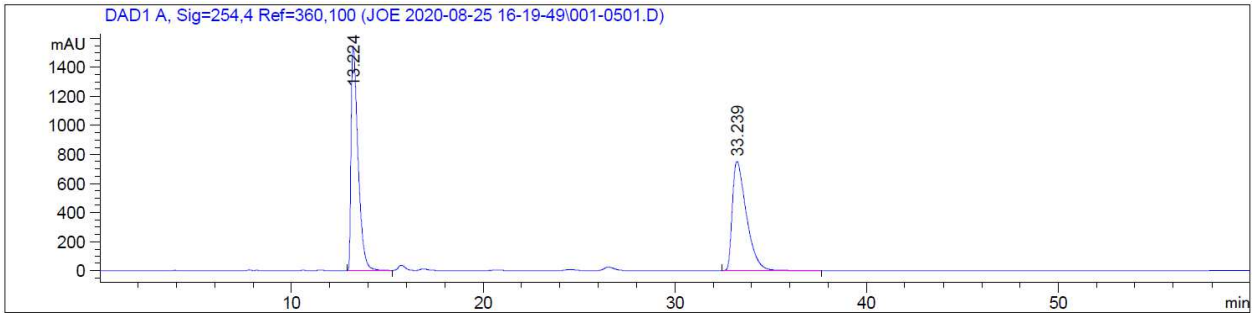
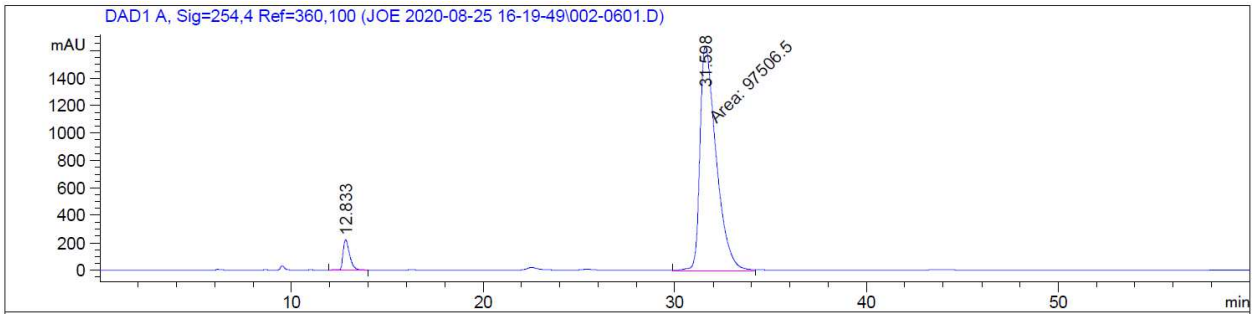
Acq. Instrument : Wasa_LC1 Location : 1
Injection Date : 8/25/2020 6:55:01 PM Inj : 1
Inj Volume : 4.000 µl
Method : C:\Chem32\1\Data\JOE 2020-08-25 16-19-49\column6 2.5%IPA 97.5% hexane 60min -0.5mL.M (Sequence Method)
Last changed : 8/25/2020 4:19:54 PM by SYSTEM
Method Info : Column6 60min-2.5% iPrOH 99% hexane-0.5mL



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

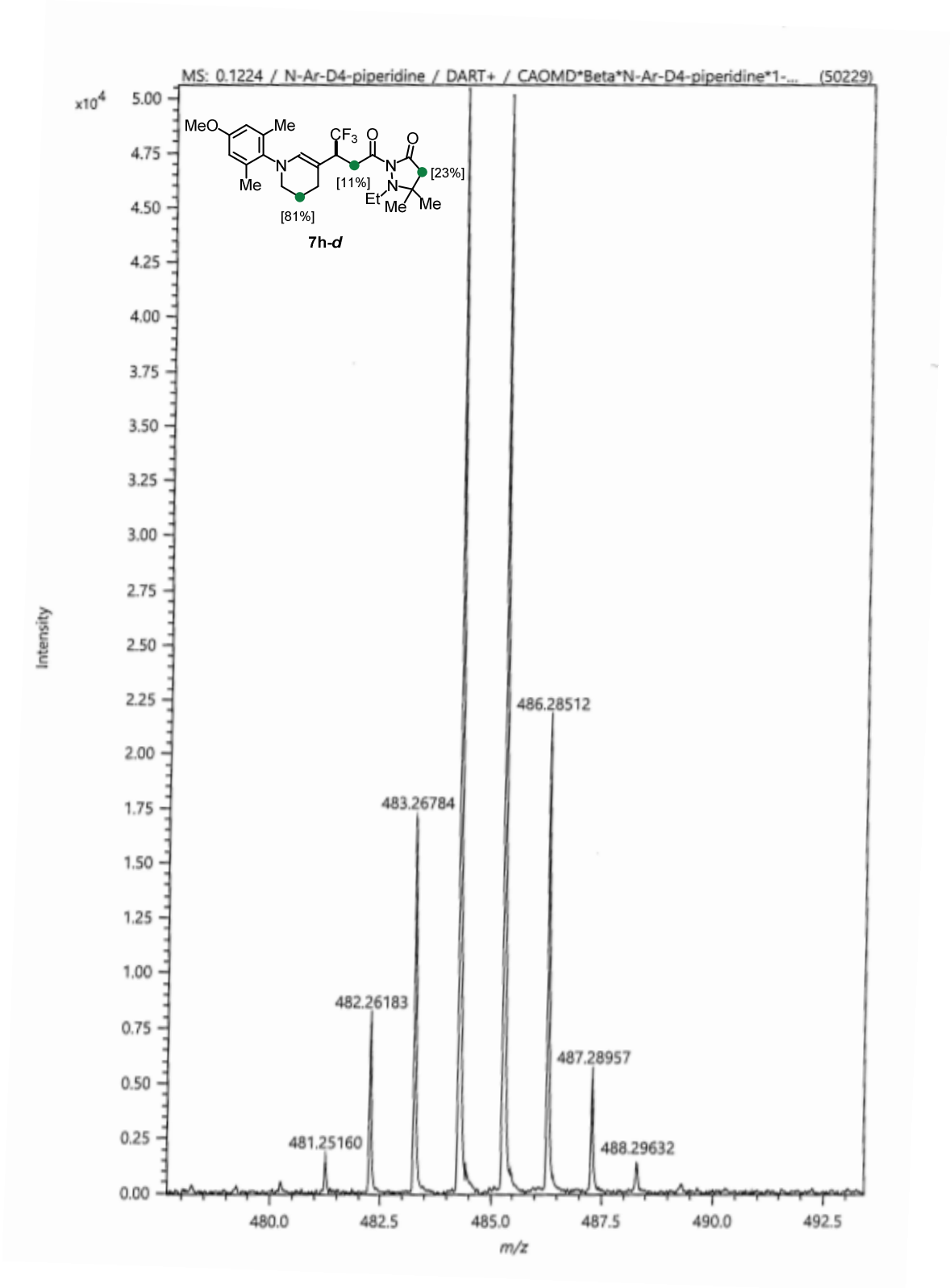
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.224	BB	0.3820	3.92641e4	1547.81995	50.5224
2	33.239	BB	0.7726	3.84521e4	751.87958	49.4776
Totals :				7.77162e4	2299.69952	

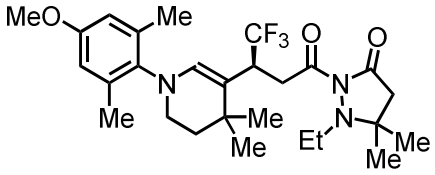
Acq. Operator : SYSTEM Seq. Line : 6
Acq. Instrument : Wasa_LC1 Location : 2
Injection Date : 8/25/2020 7:55:57 PM Inj : 1
Inj Volume : 4.000 µl
Method : C:\Chem32\1\Data\JOE 2020-08-25 16-19-49\column6 2.5%IPA 97.5% hexane 60min -0.5mL.M (Sequence Method)
Last changed : 8/25/2020 4:19:54 PM by SYSTEM
Method Info : Column6 60min-2.5% iPrOH 99% hexane-0.5mL



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.833	VB R	0.3650	5260.93115	219.42328	5.1193
2	31.598	MM	0.9911	9.75065e4	1639.71899	94.8807
Totals :				1.02767e5	1859.14227	


MS: 0.1224 / N-Ar-D4-piperidine / DART+ / CAOMD*Beta*N-Ar-D4-piperidine*1-... (50229)
x10^4
Intensity
m/z
MeO
Me
Me
N
CF3
O
O
N
N
Et
Me
Me
[81%]
[11%]
[23%]
7h-d
486.28512
483.26784
482.26183
487.28957
481.25160
488.29632
480.0
482.5
485.0
487.5
490.0
492.5



3.26g

(*S*)-1-Ethyl-5,5-dimethyl-2-(4,4,4-trifluoro-3-(1-(4-methoxy-2,6-dimethylphenyl)-4,4-dimethyl-1,4,5,6-tetrahydropyridin-3-yl)butanoyl)pyrazolidin-3-one (3.26g)

1-(4-Methoxy-2,6-dimethylphenyl)-4,4-dimethylpiperidine **3.19h** was reacted with (*E*)-1-ethyl-5,5-dimethyl-2-(4,4,4-trifluorobut-2-enoyl)pyrazolidin-3-one **3.25d** following the **General Procedure E** for 36 hours using $B(C_6F_5)_3$ (10 mol%), $Sc(OTf)_3$ (10 mol%), **L12** (12 mol%) and DCM as the solvent at 80 □. After purification by column chromatography (EtOAc:DCM = 1:16), **3.26g** was obtained as a colorless liquid (38 mg, 74%). The absolute configuration for this product was assigned in analogy to that determined for product **3.26d** (see **Section 3.6.4**).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.58 (s, 2H), 5.97 (s, 1H), 3.76 (s, 3H), 3.70 (dt, *J* = 9.8, 6.7 Hz, 1H), 3.34 (dd, *J* = 17.4, 6.2 Hz, 1H), 3.25 – 3.08 (m, 3H), 2.97 (q, *J* = 7.1 Hz, 2H), 2.60 – 2.48 (m, 2H), 2.17 (d, *J* = 9.7 Hz, 6H), 1.72 (t, *J* = 5.8 Hz, 2H), 1.29 (s, 6H), 1.14 (d, *J* = 9.1 Hz, 6H), 1.05 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 175.2, 168.4, 157.6, 138.80, 138.75, 138.1, 134.2, 127.7 (q, *J* = 280.1 Hz), 113.63, 113.56, 104.9, 60.6, 55.4, 47.2, 44.3, 44.1, 39.2, 38.5, 37.6 (q, *J* = 26.9 Hz), 31.5, 29.0, 28.7, 26.0, 25.7, 18.4, 18.3, 12.9; **^{19}F NMR (376 MHz, $CDCl_3$):** δ -69.40 (d, *J* = 9.5 Hz); **IR (neat):** ν 2959, 2927, 2842, 1744, 1711, 1637, 1466, 1442, 1374, 1302, 1250, 1228, 1150, 1123, 1096, 856, 670 cm^{-1}; **HRMS (DART):** Calcd for $C_{27}H_{39}F_3N_3O_3$ (MH^+): 510.2938; found: 510.2922; **HPLC** (CHIRACPAK IA-3; 2.5%/ 97.5% isopropanol/ hexanes, 0.2 mL/min; tr = 24.3 min (major), 28.8 min (minor); 94:6 er); **Specific Rotation $[\alpha]^{25}_D$** = -4.6° (c = 0.62, DCM).

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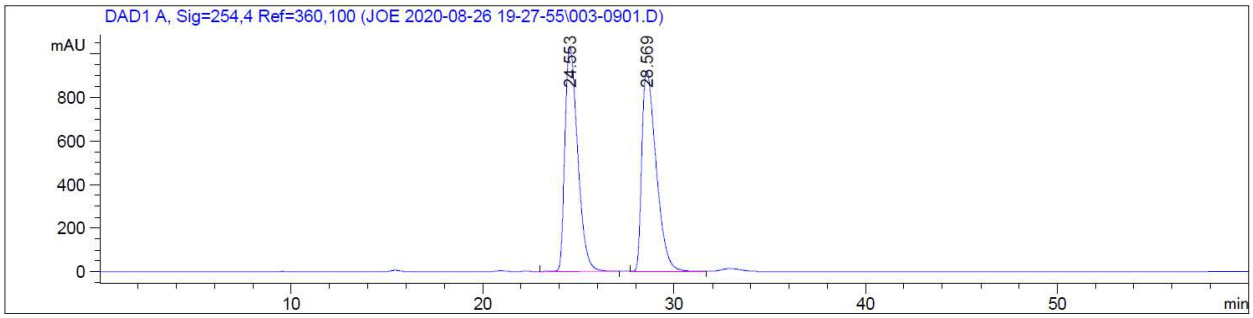
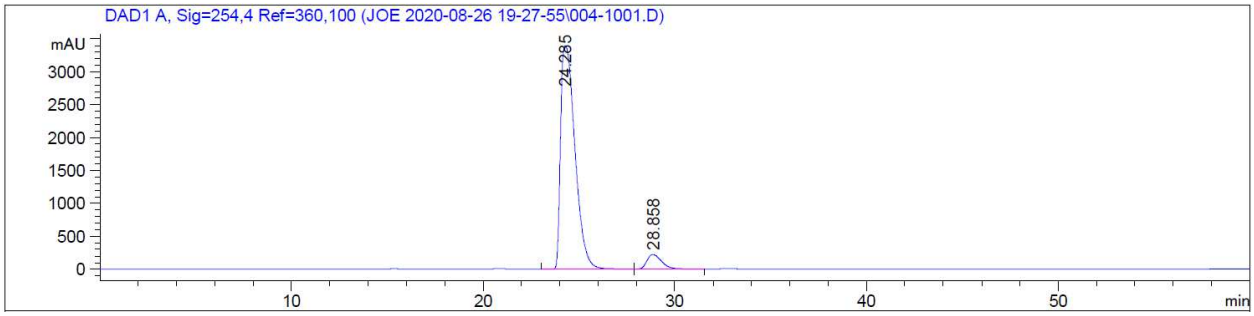
Acq. Instrument : Wasa_LC1 Location : 3
Injection Date : 8/27/2020 12:36:56 AM Inj : 1
Inj Volume : 4.000 µl
Method : C:\Chem32\1\Data\JOE 2020-08-26 19-27-55\column6 2.5%IPA 97.5% hexane 60min -0.2mL.M (Sequence Method)
Last changed : 8/26/2020 7:28:01 PM by SYSTEM
Method Info : Column6 60min-2.5% iPrOH 99% hexane-0.2mL



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

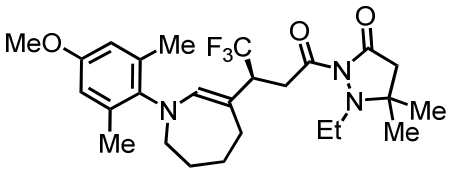
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.553	BB	0.7190	4.76944e4	1032.41467	50.0168
2	28.569	BB	0.8025	4.76623e4	919.91980	49.9832
Totals :				9.53567e4	1952.33447	

Acq. Operator : SYSTEM Seq. Line : 10
Acq. Instrument : Wasa_LC1 Location : 4
Injection Date : 8/27/2020 1:37:52 AM Inj : 1
Inj Volume : 4.000 µl
Method : C:\Chem32\1\Data\JOE 2020-08-26 19-27-55\column6 2.5%IPA 97.5% hexane 60min -0.2mL.M (Sequence Method)
Last changed : 8/26/2020 7:28:01 PM by SYSTEM
Method Info : Column6 60min-2.5% iPrOH 99% hexane-0.2mL



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.285	BB	0.8178	1.76359e5	3396.43530	93.7370
2	28.858	BB	0.8209	1.17834e4	222.13094	6.2630
Totals :				1.88143e5	3618.56624	



3.26h

(*S*)-1-Ethyl-5,5-dimethyl-2-(4,4,4-trifluoro-3-(1-(4-methoxy-2,6-dimethylphenyl)-4,5,6,7-tetrahydro-1*H*-azepin-3-yl)butanoyl)pyrazolidin-3-one (3.26h)

1-(4-Methoxy-2,6-dimethylphenyl)azepane **3.19u** was reacted with (*E*)-1-ethyl-5,5-dimethyl-2-(4,4,4-trifluorobut-2-enoyl)pyrazolidin-3-one **3.25d** following the **General Procedure E** for 24 hours using $B(C_6F_5)_3$ (10 mol%), $Sc(OTf)_3$ (10 mol%), **L12** (12 mol%) and DCM as the solvent. After purification by column chromatography (ethyl ether:hexanes = 1:1) **3.26h** was obtained as a colorless liquid (39 mg, 78%). The absolute configuration for this product was assigned in analogy to that determined for product **3.26d** (see **Section 3.6.4**).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.55 (s, 2H), 5.84 (s, 1H), 3.75 (s, 3H), 3.40 – 3.22 (m, 4H), 3.15 (d, *J* = 12.8 Hz, 1H), 3.01 – 2.90 (m, 2H), 2.61 – 2.50 (m, 2H), 2.41 – 2.25 (m, 2H), 2.20 (d, *J* = 4.3 Hz, 6H), 1.84 – 1.70 (m, 4H), 1.28 (d, *J* = 3.6 Hz, 6H), 1.04 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 175.4, 168.1, 157.4, 141.8, 140.5, 138.1, 137.9, 127.7 (q, *J* = 280.8 Hz), 113.6, 113.5, 104.1, 60.6, 55.4, 54.7, 47.2, 46.7 (q, *J* = 26.7 Hz), 44.0, 34.5, 30.5, 29.3, 26.8, 25.9, 18.9, 18.8, 13.0; **^{19}F NMR (470 MHz, $CDCl_3$):** δ -70.17 (d, *J* = 9.1 Hz); **IR (neat):** ν 2925, 2849, 1744, 1709, 1648, 1602, 1485, 1466, 1442, 1374, 1308, 1261, 1207, 1152, 1104, 1066, 1031, 895, 732, 701, 618 cm^{-1}; **HRMS (DART):** Calcd for $C_{26}H_{37}F_3N_3O_3$ (MH^+): 496.2782; found: 496.2774; **HPLC** (CHIRACPAK IA-3; 5%/ 95% isopropanol/ hexanes, 1.0 mL/min; tr = 4.2 min (minor), 11.0 min (major); 94:6 er); **Specific Rotation $[\alpha]^{25}_D$** = -17.3° (c = 0.47, DCM).

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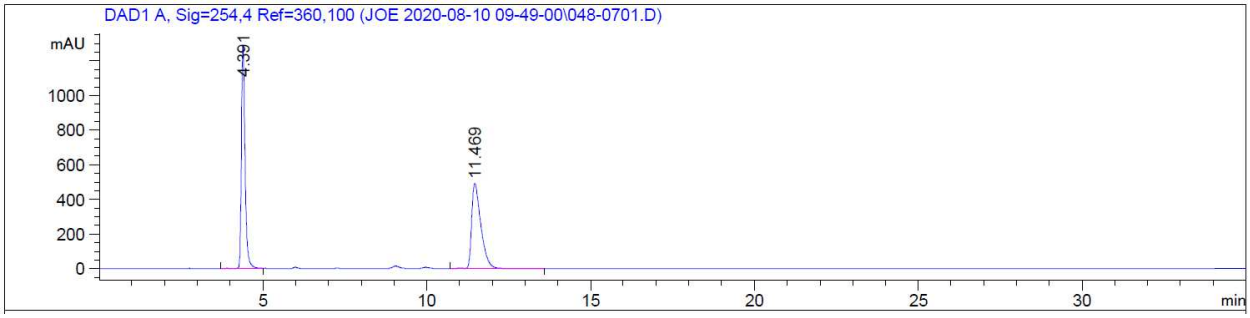
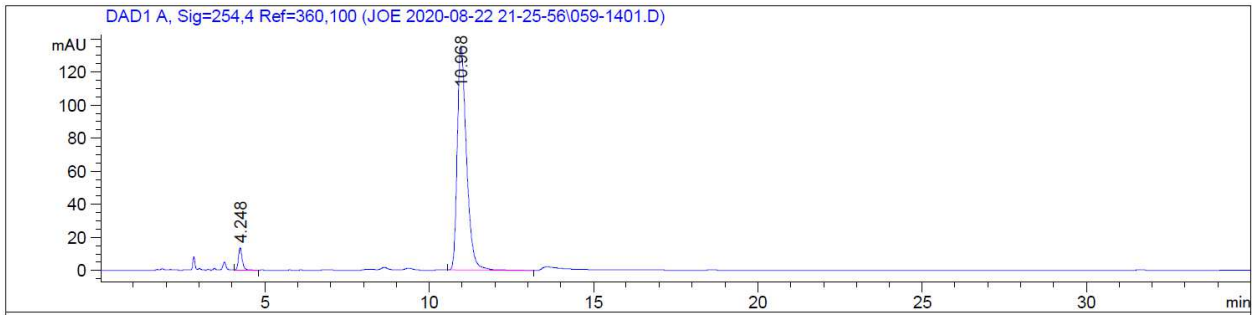
Acq. Instrument : Wasa_LC1 Location : 48
Injection Date : 8/10/2020 3:57:11 PM Inj : 1
Inj Volume : 4.000 µl
Method : C:\Chem32\1\Data\JOE 2020-08-10 09-49-00\column6 5%IPA 95% hexane 35min-1.0mL.M (Sequence Method)
Last changed : 8/10/2020 9:49:05 AM by SYSTEM
Method Info : Column6 35min-5% iPrOH 95% hexane-1.0mL



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

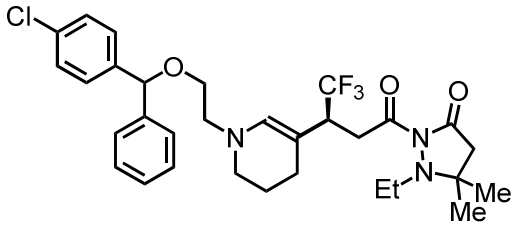
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.391	VB R	0.1184	1.00388e4	1293.51587	50.9692
2	11.469	VB R	0.2963	9656.99121	491.59241	49.0308
Totals :				1.96957e4	1785.10828	

Acq. Operator : SYSTEM Seq. Line : 14
Acq. Instrument : Wasa_LC1 Location : 59
Injection Date : 8/23/2020 9:50:57 AM Inj : 1
Inj Volume : 4.000 µl
Method : C:\Chem32\1\Data\JOE 2020-08-22 21-25-56\column6 5%IPA 95% hexane 35min-1.0mL.M (Sequence Method)
Last changed : 8/22/2020 9:26:02 PM by SYSTEM
Method Info : Column6 35min-5% iPrOH 95% hexane-1.0mL



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.248	VB	0.1245	108.70381	13.42023	3.9333
2	10.968	BB	0.2970	2654.95752	135.25128	96.0667
Totals :				2763.66133	148.67151	



3.26i

2-((3*S*)-3-(1-(2-((4-Chlorophenyl)(phenyl)methoxy)ethyl)-1,4,5,6-tetrahydropyridin-3-yl)-4,4,4-trifluorobutanoyl)-1-ethyl-5,5-dimethylpyrazolidin-3-one (3.26i)

1-(2-((4-Chlorophenyl)(phenyl)methoxy)ethyl)piperidine **3.19v** was reacted with (*E*)-1-ethyl-5,5-dimethyl-2-(4,4,4-trifluorobut-2-enoyl)pyrazolidin-3-one **3.25d** following the **General Procedure General Procedure E** for 24 hours using $B(C_6F_5)_3$ (20 mol%), $Sc(OTf)_3$ (10 mol%), **L10** (12 mol%) and DCM as the solvent at 80 □. ^{1}H NMR and ^{19}F NMR analysis of the unpurified product mixture using mesitylene and perfluorobenzene as the internal standard revealed that the diastereomeric ratio was 1.0:1. After purification by column chromatography (EtOAc:hexanes = 1:4), **3.26i** was obtained as an inseparable mixture of diastereomers (31 mg, 53%). The absolute configuration for this product was assigned in analogy to that determined for product **3.26d** (see **Section 3.6.4**).

^{1}H NMR (400 MHz, $CDCl_3$, *peaks from diastereomers are merged*): δ 7.33 – 7.20 (m, 8H), 5.96 (s, 1H), 5.27 (s, 1H), 3.48 – 3.40 (m, 2H), 3.39 – 3.27 (m, 2H), 3.14 – 2.83 (m, 7H), 2.61 – 2.48 (m, 2H), 2.03 (t, *J* = 6.2 Hz, 2H), 1.83 – 1.67 (m, 2H), 1.25 (d, *J* = 9.6 Hz, 6H), 1.01 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 175.3, 168.3, 141.88, 141.87, 141.0, 136.9, 133.3, 128.7, 128.6, 128.34, 128.31, 127.8, 127.6 (q, *J* = 281.3 Hz), 127.00, 126.96, 97.8, 83.4, 67.55, 67.53, 60.6, 55.0, 47.2, 47.0, 45.0 (q, *J* = 27.1 Hz), 44.1, 34.2, 26.0, 25.7, 22.8, 22.6, 12.9; **^{19}F NMR (470 MHz, $CDCl_3$):** δ -69.70 – -69.87 (m); **IR (neat):** ν 2919, 2849, 1742, 1710, 1654, 1513, 1488, 1465, 1450, 1373, 1337, 1303, 1256, 1237, 1177, 1138, 1096, 1038, 812, 757, 718, 616 cm^{-1};

HRMS (DART): Calcd for $C_{31}H_{38}ClF_3N_3O_3$ (MH^+): 592.2548; found: 592.2542; **HPLC** (CHIRACPAK AD-H; 5%/ 95% isopropanol/ hexanes, 0.2 mL/min; tr = 49.2 min (major1), 53.6 min (major2), 61.7 min (minor1), 65.5 min (minor2); 90:10 er); **Specific Rotation** $[\alpha]^{25}_{D}$ = +2.0° (c = 0.50, DCM).

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Acq. Instrument : Wasa_LC1                         Location :   5
Injection Date  : 9/20/2020 11:01:30 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2020-09-20 17-02-28\column1 5% IPA 95% hexane 80min-0.
                  2mL.M
Last changed    : 9/20/2020 5:02:34 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2020-09-20 17-02-28\column1 5% IPA 95% hexane 80min-0.
                  2mL.M (Sequence Method)
Last changed    : 9/21/2020 10:31:35 AM by SYSTEM
                  (modified after loading)
Method Info     : 80min-5% iPrOH 95% hexane-0.2mL
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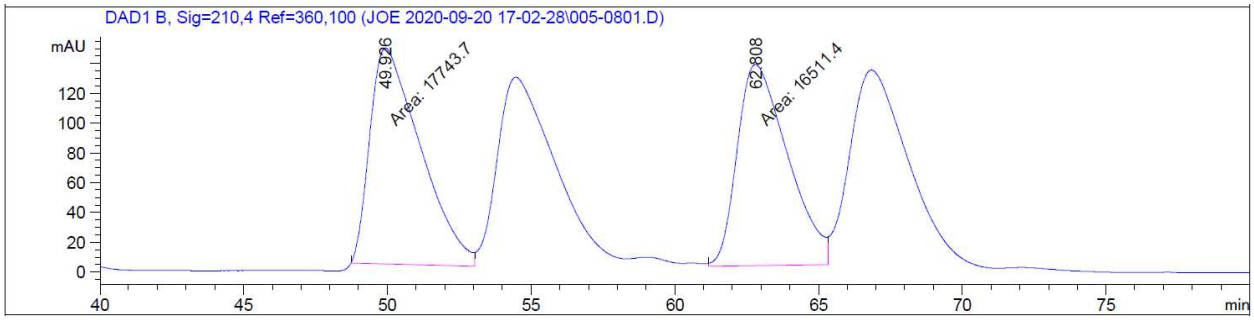

Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	49.926	MM	2.0423	1.77437e4	144.79956	51.7986
2	62.808	MM	2.0391	1.65114e4	134.95860	48.2014
Totals :				3.42551e4	279.75816	

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Acq. Operator   : SYSTEM                          Seq. Line :  10
Acq. Instrument : Wasa_LC1                         Location :   9
Injection Date  : 9/21/2020 1:43:24 AM                 Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2020-09-20 17-02-28\column1 5% IPA 95% hexane 80min-0.
                  2mL.M
Last changed    : 9/20/2020 5:02:34 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2020-09-20 17-02-28\column1 5% IPA 95% hexane 80min-0.
                  2mL.M (Sequence Method)
Last changed    : 9/21/2020 10:31:35 AM by SYSTEM
                  (modified after loading)
Method Info     : 80min-5% iPrOH 95% hexane-0.2mL
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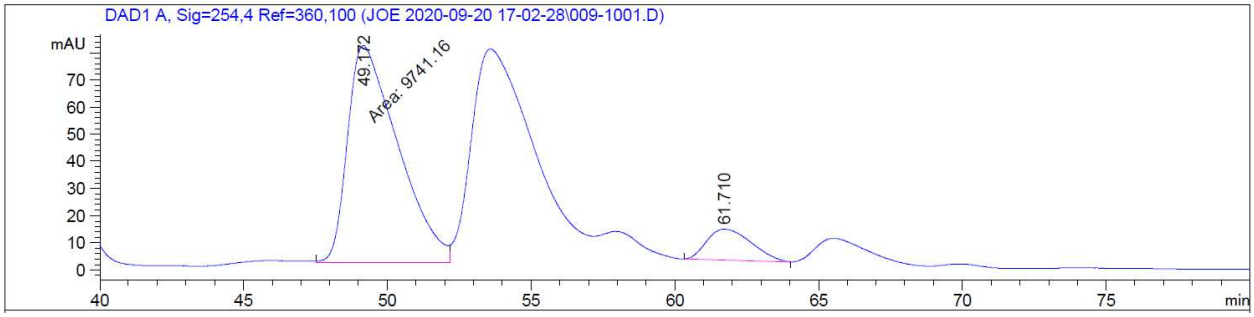

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	49.172	MM	2.0318	9741.15723	79.90520	88.8697
2	61.710	BB	1.2890	1220.00977	11.37721	11.1303
Totals :				1.09612e4	91.28240	

```
Acq. Operator   : SYSTEM                          Seq. Line :   8
Acq. Instrument : Wasa_LC1                         Location :   5
Injection Date  : 9/20/2020 11:01:30 PM                Inj :   1
                                                Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2020-09-20 17-02-28\column1 5% IPA 95% hexane 80min-0.
                  2mL.M
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Analysis Method : C:\Chem32\1\Data\JOE 2020-09-20 17-02-28\column1 5% IPA 95% hexane 80min-0.
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Method Info     : 80min-5% iPrOH 95% hexane-0.2mL
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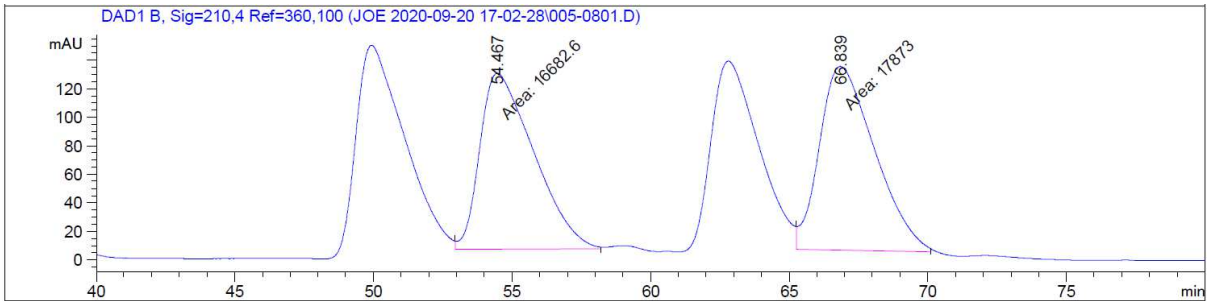

Signal 2: DAD1 B, Sig=210,4 Ref=360,100

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1	54.467	MM	2.2531	1.66826e4	123.40290	48.2776
2	66.839	MM	2.3115	1.78730e4	128.87001	51.7224
Totals :				3.45555e4	252.27291	

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Acq. Operator   : SYSTEM                          Seq. Line :  10
Acq. Instrument : Wasa_LC1                         Location :   9
Injection Date  : 9/21/2020 1:43:24 AM                Inj :   1
                                                 Inj Volume : 4.000 µl
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                  2mL.M
Last changed    : 9/20/2020 5:02:34 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2020-09-20 17-02-28\column1 5% IPA 95% hexane 80min-0.
                  2mL.M (Sequence Method)
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Method Info     : 80min-5% iPrOH 95% hexane-0.2mL
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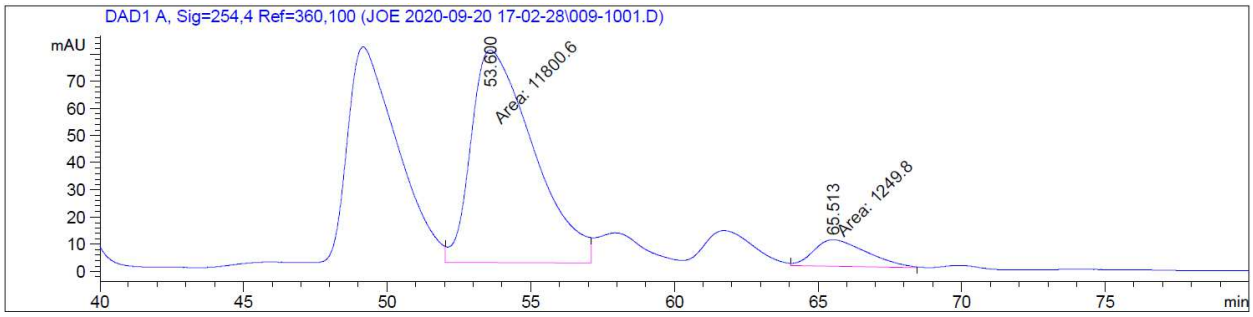
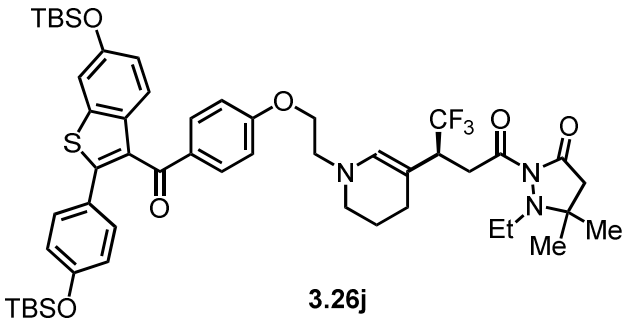


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	53.600	MM	2.5154	1.18006e4	78.18829	90.4233
2	65.513	MM	2.1369	1249.79602	9.74771	9.5767
Totals :				1.30504e4	87.93600	



3.26j

(*S*)-2-(3-(1-(2-(4-(6-((*tert*-Butyldimethylsilyl)oxy)-2-(4-((*tert*-butyldimethylsilyl)oxy) phenyl)benzo[*b*]thiophene-3-carbonyl)phenoxy)ethyl)-1,4,5,6-tetrahydropyridin-3-yl)-4,4,4-trifluorobutanoyl)-1-ethyl-5,5-dimethylpyrazolidin-3-one (3.26j)

(6-((*tert*-Butyldimethylsilyl)oxy)-2-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)benzo[*b*]thiophen -3-yl)(4-(2-(piperidin-1-yl)ethoxy)phenyl)methanone **3.19q** was reacted with (*E*)-1-ethyl-5,5-dimethyl-2-(4,4,4-trifluorobut-2-enoyl)pyrazolidin-3-one **3.25d** following the **General Procedure General Procedure E** for 24 hours using $B(C_6F_5)_3$ (20 mol%), $Sc(OTf)_3$ (10 mol%), **L10** (12 mol%) and DCM as the solvent at 80 □. After purification by column chromatography (EtOAc:hexanes = 1:4), **3.26j** was obtained as a white solid (55 mg, 57%). The absolute configuration for this product was assigned in analogy to that determined for product **3.26d** (see **Section 3.6.4**).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.9 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.29 – 7.22 (m, 3H), 6.87 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.70 (d, *J* = 9.0 Hz, 2H), 6.66 (d, *J* = 8.6 Hz, 2H), 5.95 (s, 1H), 3.93 (t, *J* = 5.6 Hz, 2H), 3.40 – 3.30 (m, 2H), 3.22 – 3.12 (m, 2H), 3.11 – 3.03 (m, 1H), 3.00 – 2.93 (m, 2H), 2.91 (q, *J* = 7.1 Hz, 2H), 2.59 – 2.48 (m, 2H), 2.01 (t, *J* = 6.3 Hz, 2H), 1.85 – 1.69 (m, 2H), 1.25 (d, *J* = 10.2 Hz, 6H), 1.02 – 0.98 (m, 12H), 0.92 (s, 9H), 0.22 (s, 6H), 0.11 (s, 6H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 193.3, 175.3, 168.3, 162.8, 156.2, 153.6, 143.4, 140.0, 136.5, 134.6, 132.4, 130.7, 130.6, 130.4, 127.5 (q, *J* = 281.1 Hz), 126.9, 124.0, 120.4, 119.4, 114.1, 112.2, 99.3,

66.6, 60.6, 54.1, 47.2, 47.1, 44.9 (q, J = 27.2 Hz), 43.9, 34.2, 30.4, 29.8, 25.8, 25.7, 22.7, 22.5, 18.4, 18.3, 12.9, -4.2, -4.4; **^{19}F NMR (376 MHz, $CDCl_3$):** δ -69.86 (d, J = 9.2 Hz); **IR (neat):** ν 2952, 2927, 2856, 1744, 1710, 1655, 1597, 1530, 1465, 1304, 1255, 1165, 1137, 1038, 942, 909, 838, 642 cm^{-1}; **HRMS (DART):** Calcd for $C_{51}H_{69}F_3N_3O_6SSi_2$ (MH^+): 964.4392; found: 964.4392; **HPLC** (CHIRACPAK IA-3; 5%/ 95% isopropanol/ hexanes, 1.0 mL/min; tr = 11.8 min (minor), 15.7 min (major); 95:5 er); **Specific Rotation $[\alpha]^{25}_D$** = -4.6° (c = 0.82, DCM).

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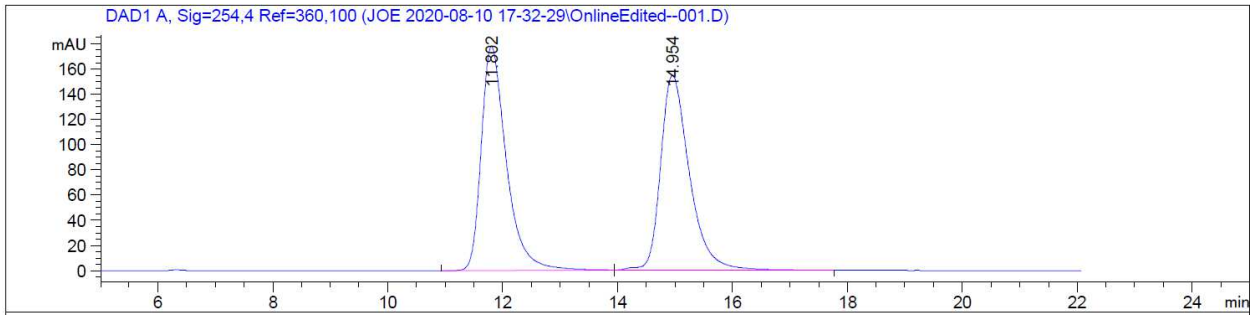

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

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1	11.802	BB	0.4620	5396.38525	177.85497	50.0678
2	14.954	BB	0.5279	5381.77783	154.66997	49.9322
Totals :				1.07782e4	332.52493	

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Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Wasa_LC1                         Location :   84
Injection Date  : 8/20/2020 10:21:48 PM                Inj :   1
                                                 Inj Volume : 4.000 µl
Acq. Method     : C:\Chem32\1\Data\JOE 2020-08-20 21-53-45\column6 5%IPA 95% hexane 25min-1.
                  0mL.M
Last changed    : 8/20/2020 9:53:51 PM by SYSTEM
Analysis Method : C:\Chem32\1\Data\JOE 2020-08-20 21-53-45\column6 5%IPA 95% hexane 25min-1.
                  0mL.M (Sequence Method)
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Method Info     : Column6 25min-5% iPrOH 95% hexane-1.0mL
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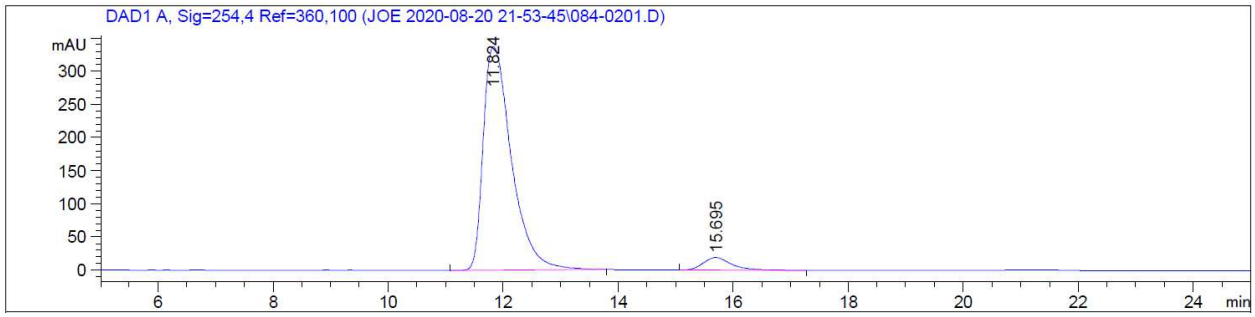
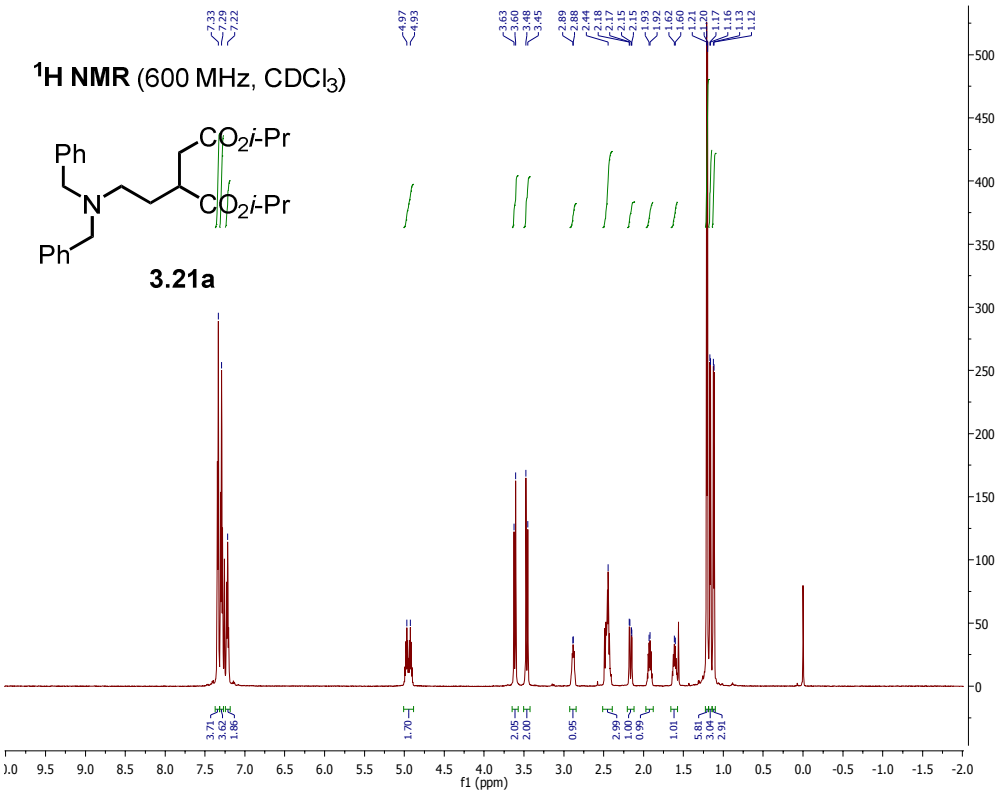
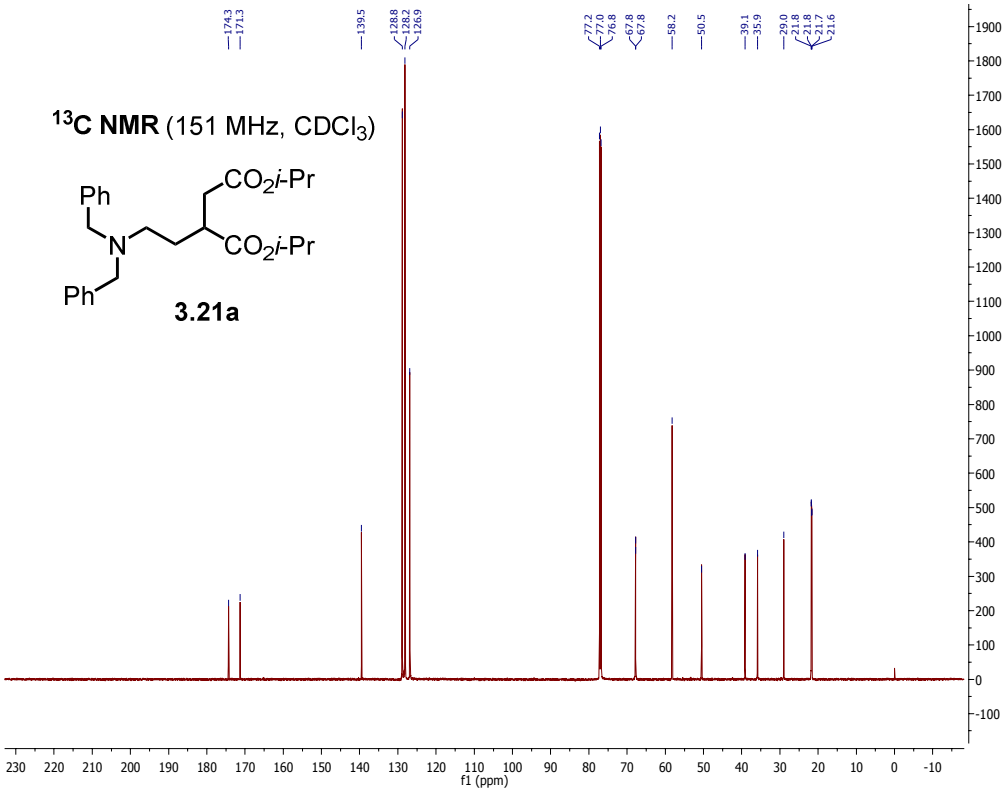


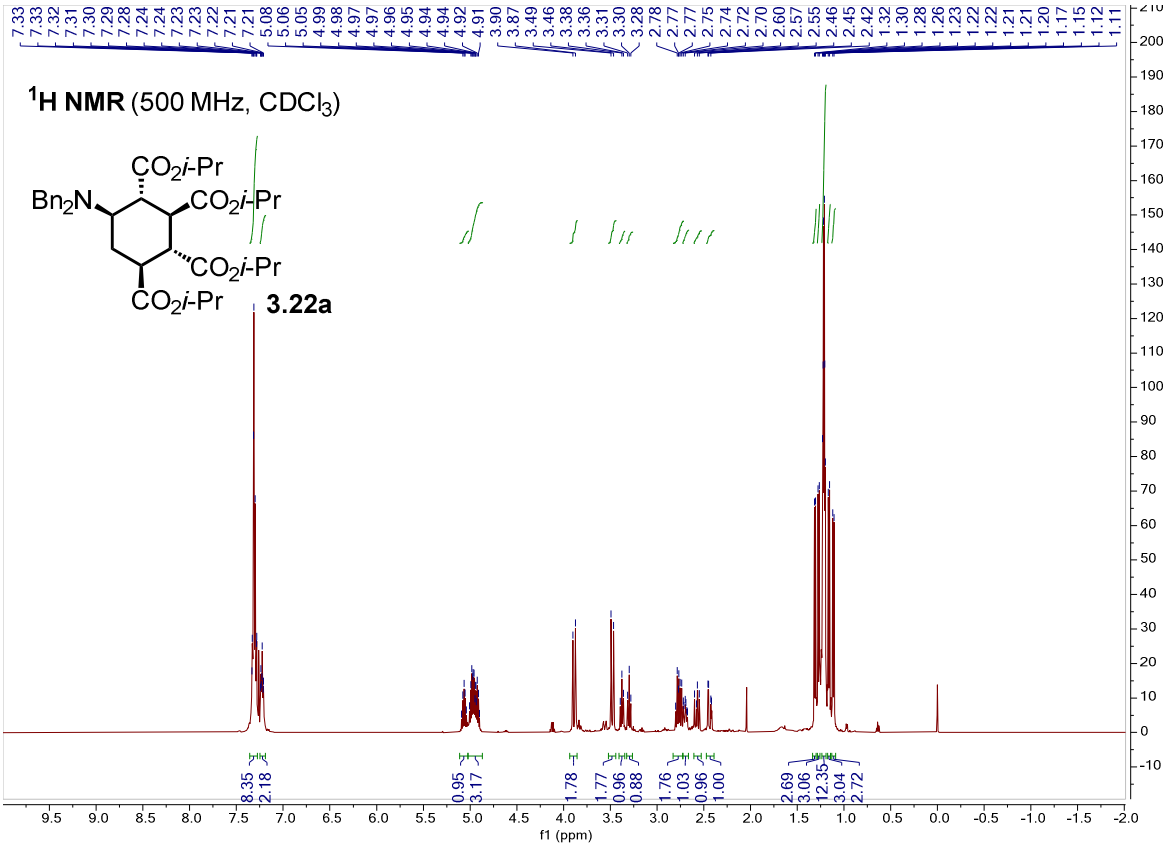
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

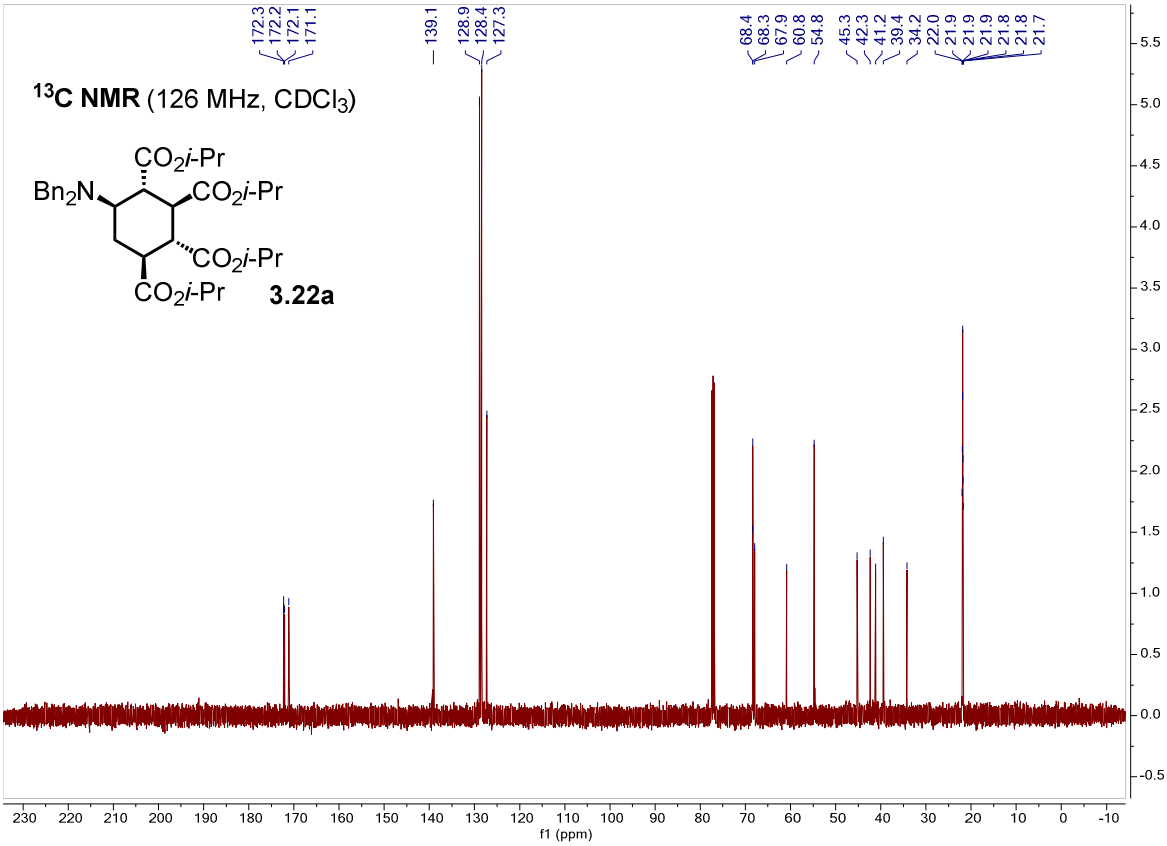
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.824	BB	0.4976	1.14902e4	337.18747	94.7035
2	15.695	BB	0.4999	642.61816	19.03380	5.2965
Totals :				1.21328e4	356.22127	

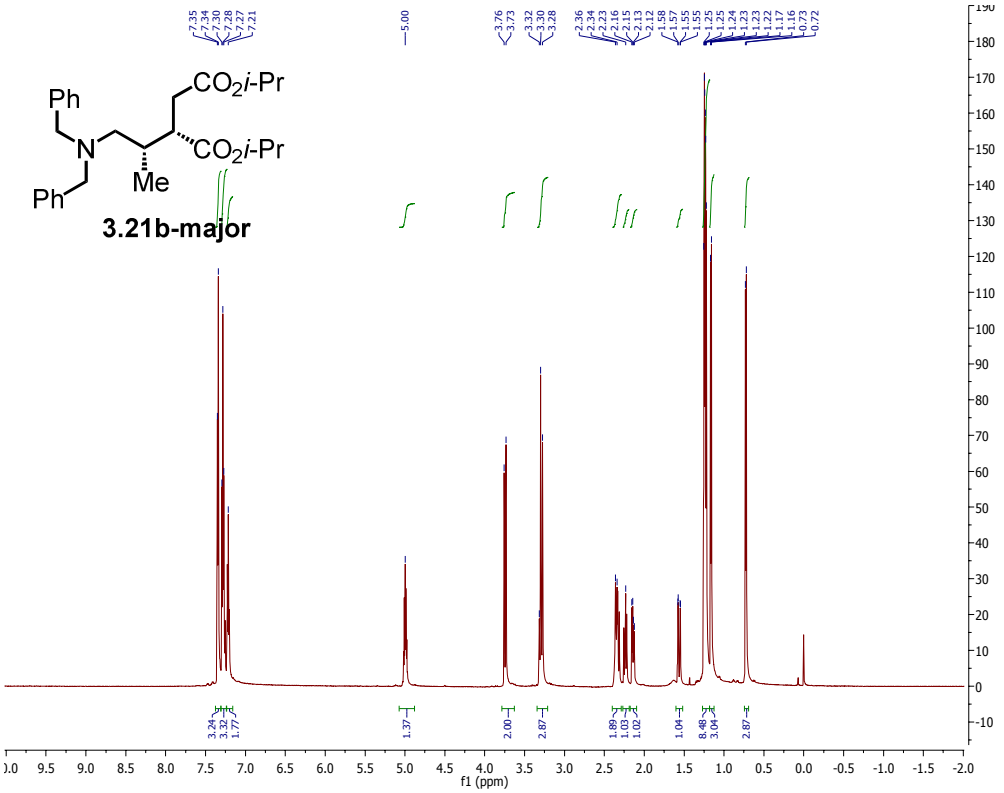
3.6.8. NMR Spectra for New Compounds






^{1}H NMR (500 MHz, CDCl$_3$)
Bn$_2$N
CO$_2$*i*-Pr
CO$_2$*i*-Pr
CO$_2$*i*-Pr
CO$_2$*i*-Pr
3.22a
f1 (ppm)


^{13}C NMR (126 MHz, CDCl$_3$)
Bn$_2$N
CO$_2$*i*-Pr
CO$_2$*i*-Pr
CO$_2$*i*-Pr
CO$_2$*i*-Pr
3.22a
f1 (ppm)


Ph
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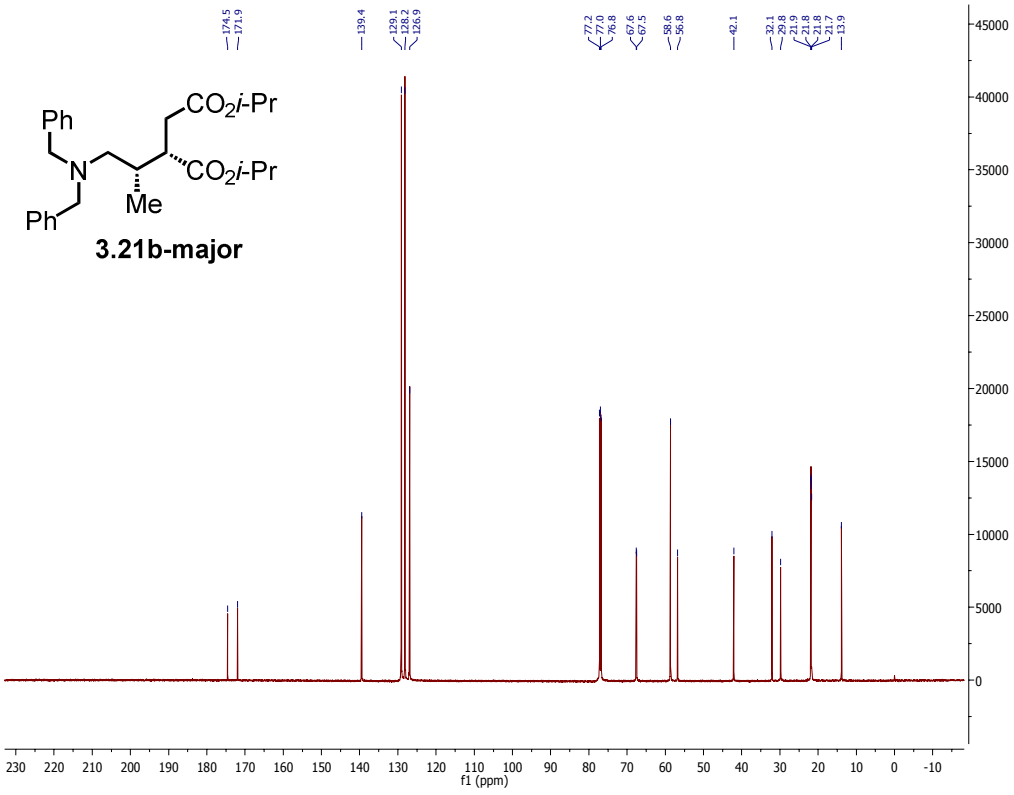
Me
Ph
CO2i-Pr
CO2i-Pr
3.21b-major
f1 (ppm)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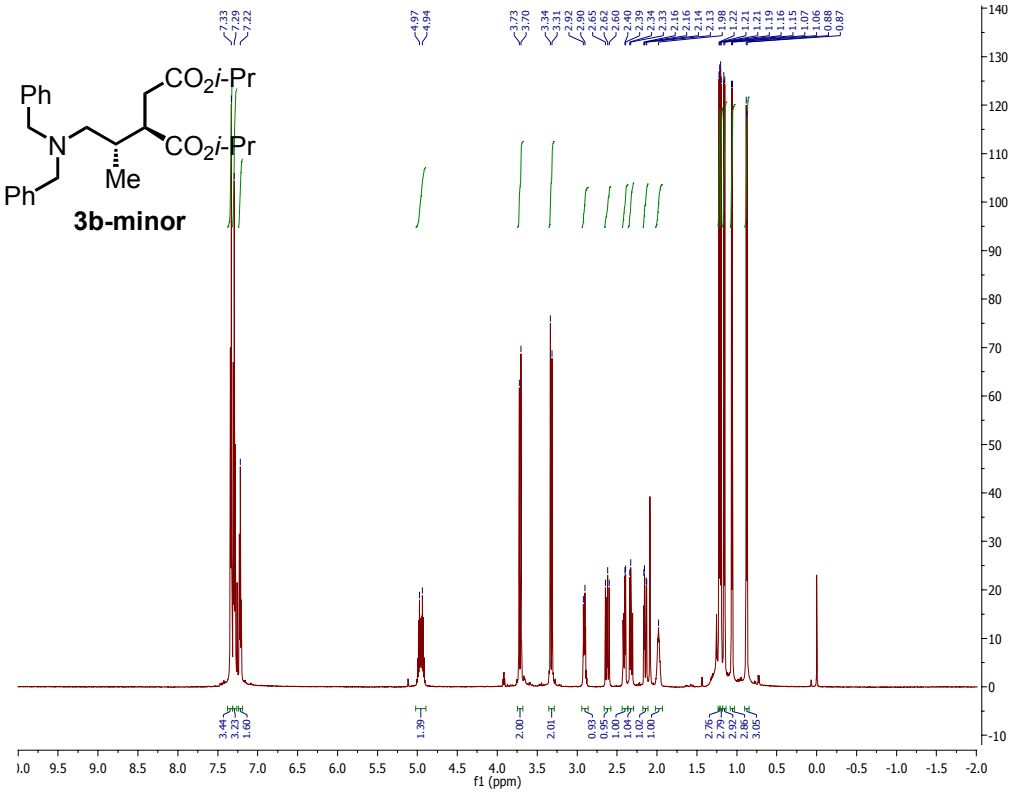
Me
Ph
CO2i-Pr
CO2i-Pr
3.21b-major
f1 (ppm)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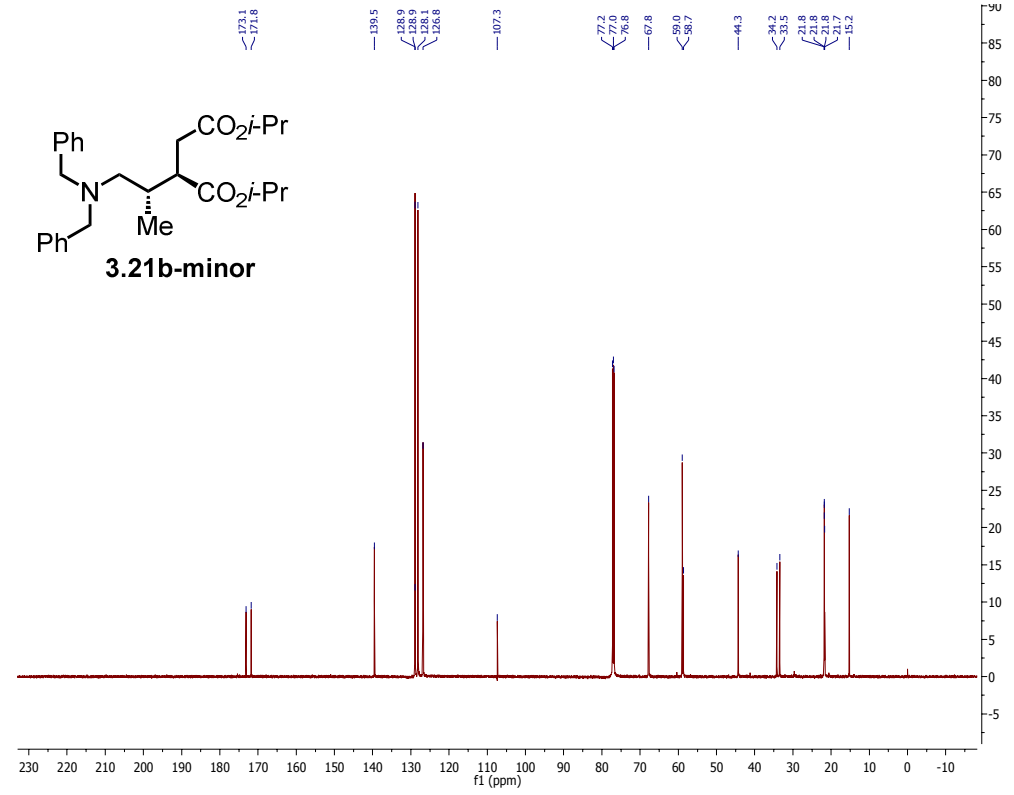
Me
Ph
CO2i-Pr
CO2i-Pr
3b-minor
f1 (ppm)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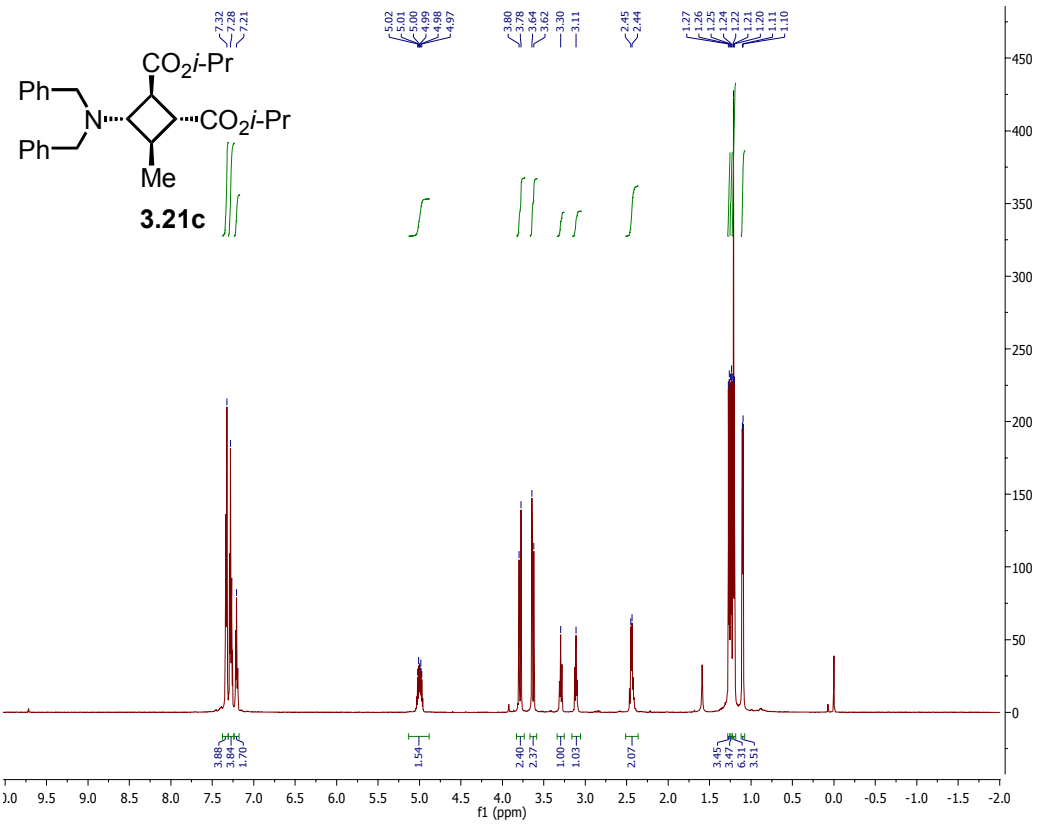
N
Me
Ph
CO2i-Pr
CO2i-Pr
3.21b-minor
f1 (ppm)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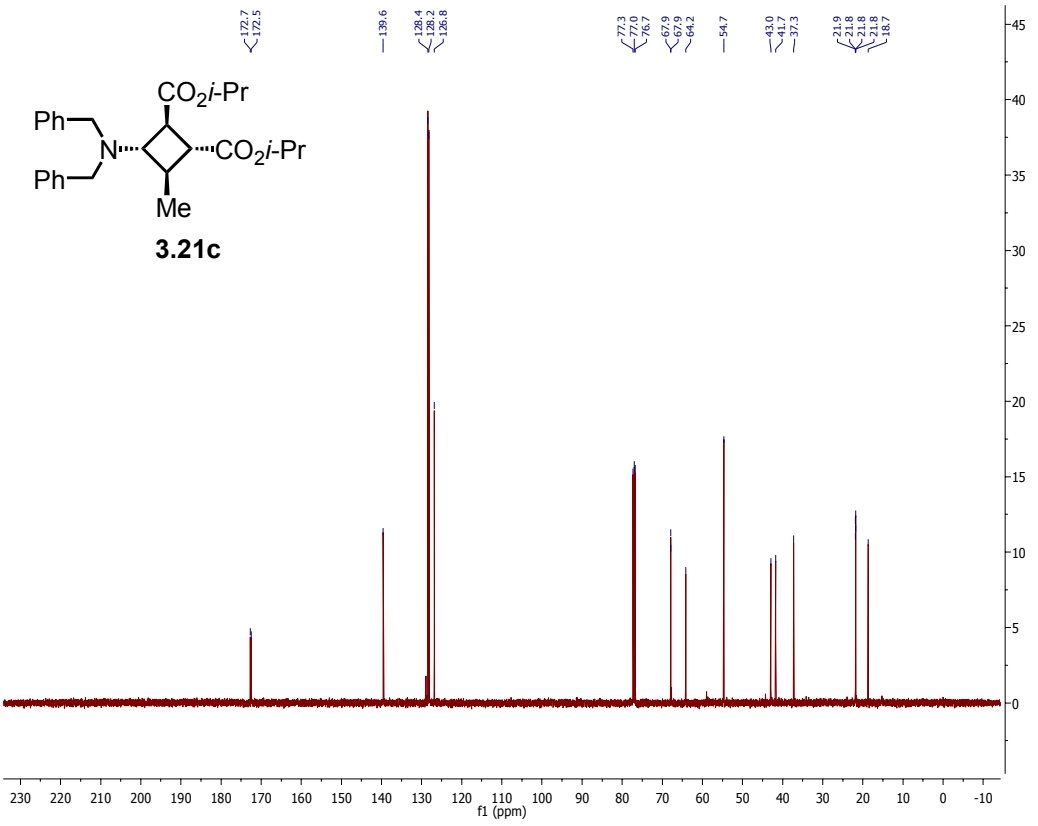
CO2i-Pr
Ph
Me
3.21c
f1 (ppm)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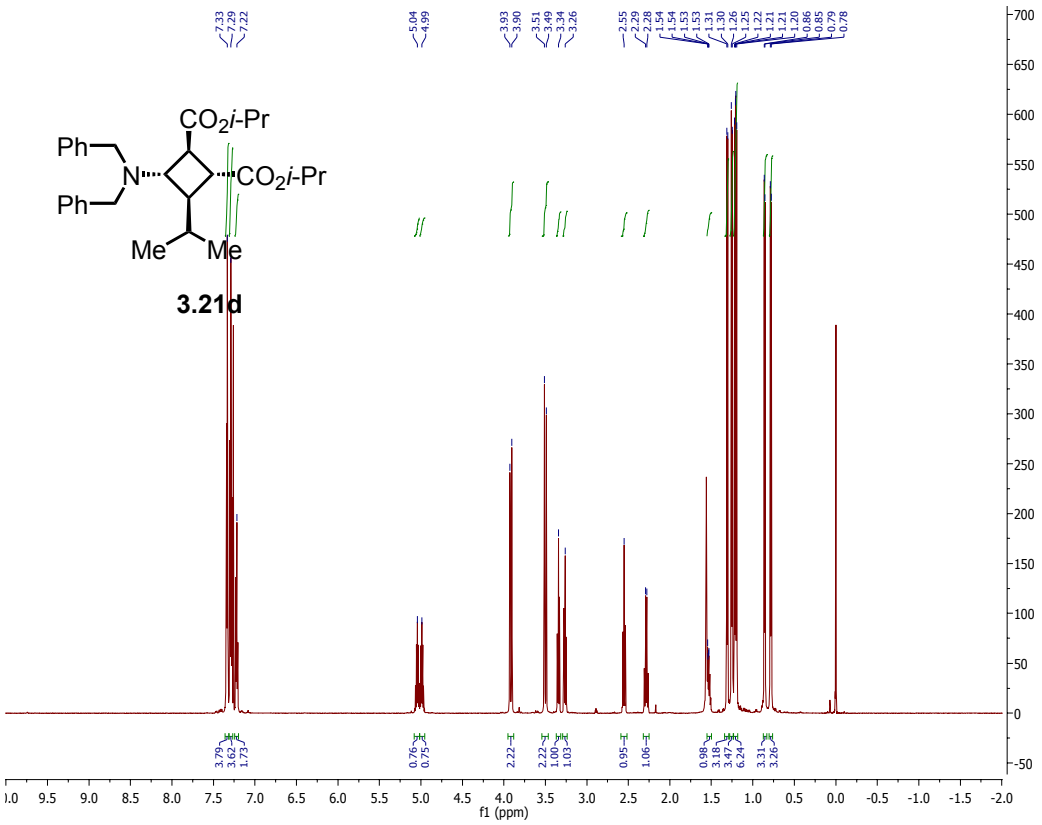
CO2i-Pr
Ph
Me
3.21c
f1 (ppm)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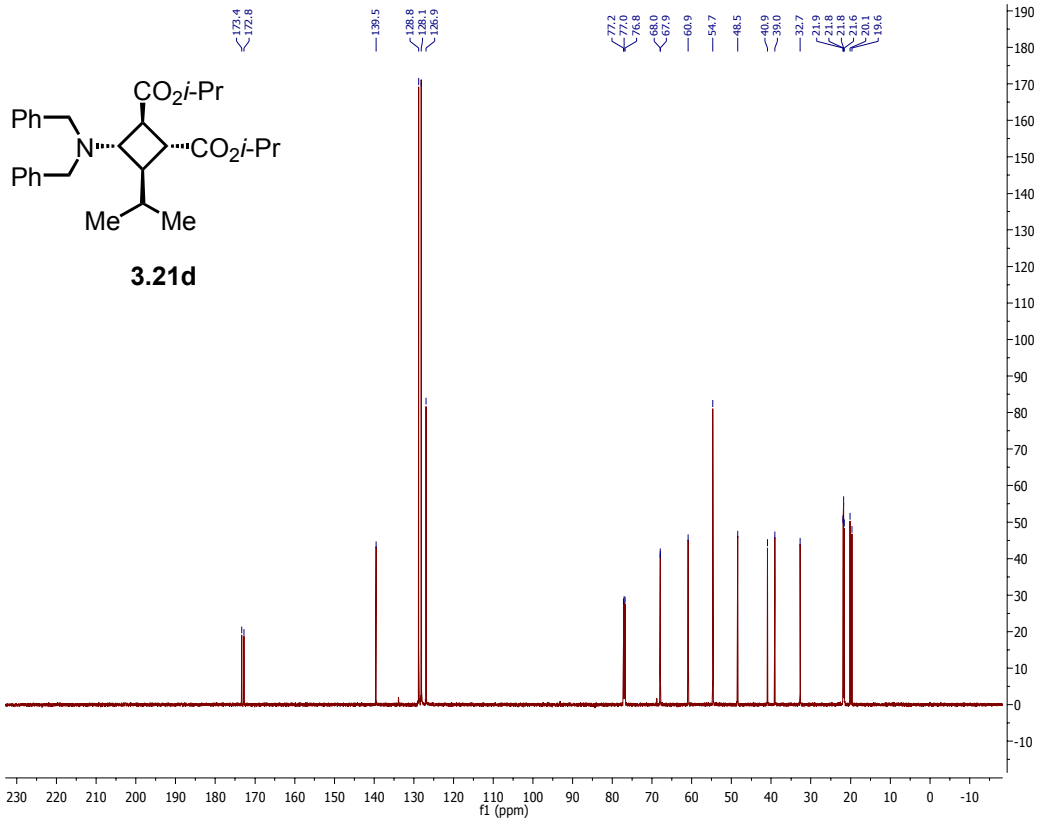
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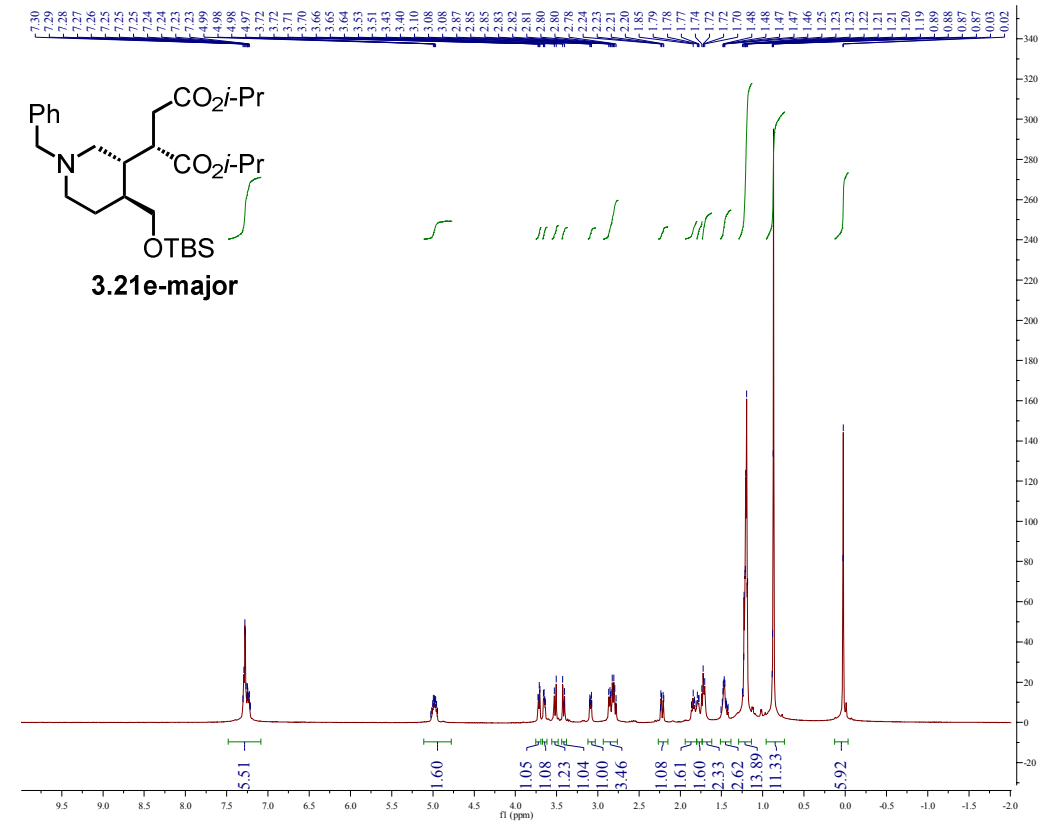
N
CO2i-Pr
Ph
Me
Me
3.21d
f1 (ppm)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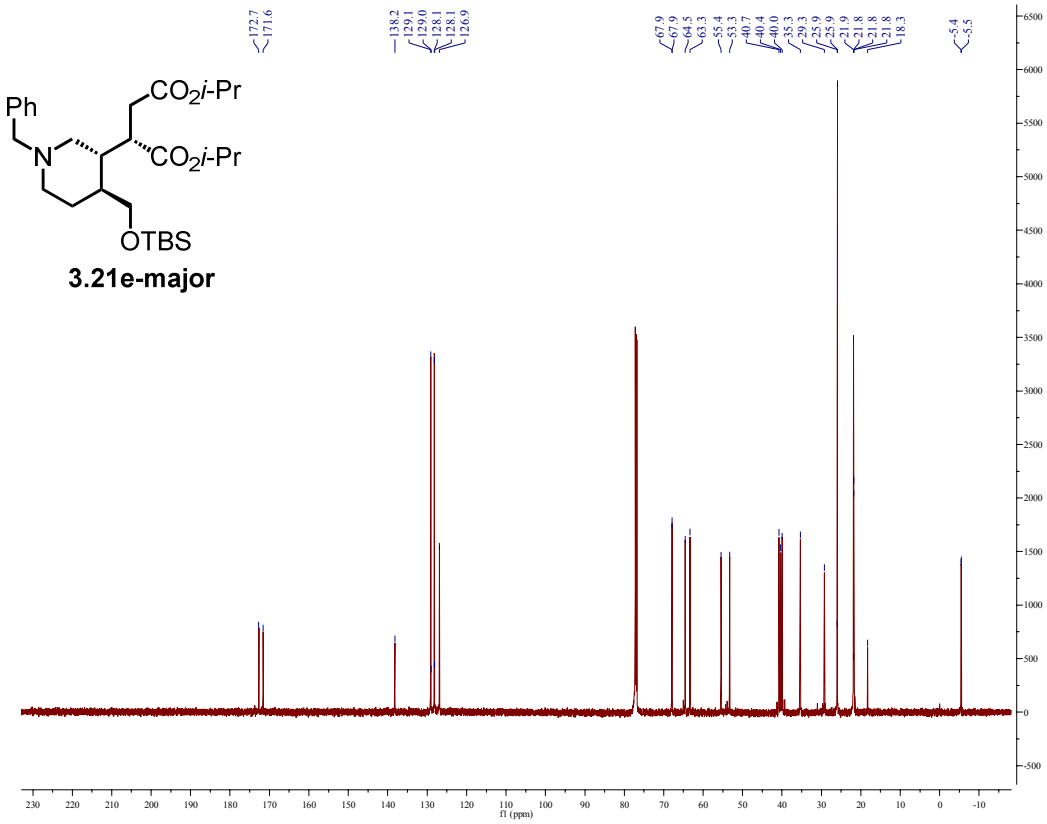
CO2i-Pr
CO2i-Pr
OTBS
3.21e-major
f1 (ppm)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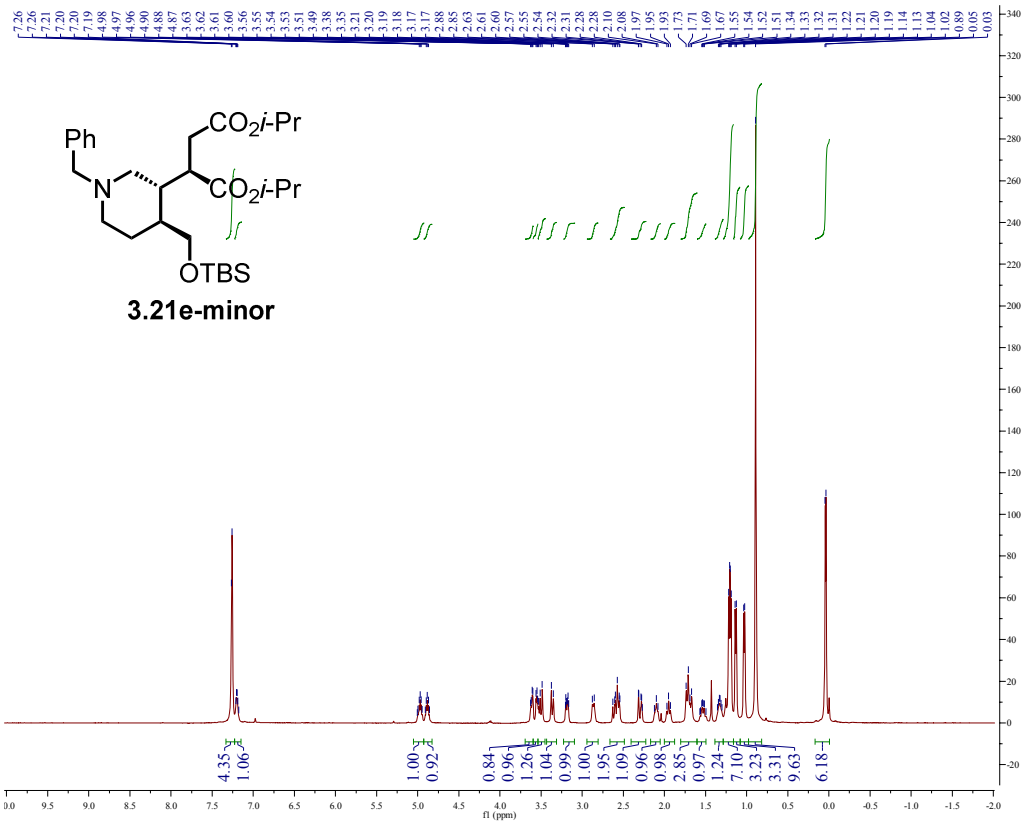
CO2i-Pr
CO2i-Pr
OTBS
3.21e-major
f1 (ppm)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CO2i-Pr
CO2i-Pr
OTBS
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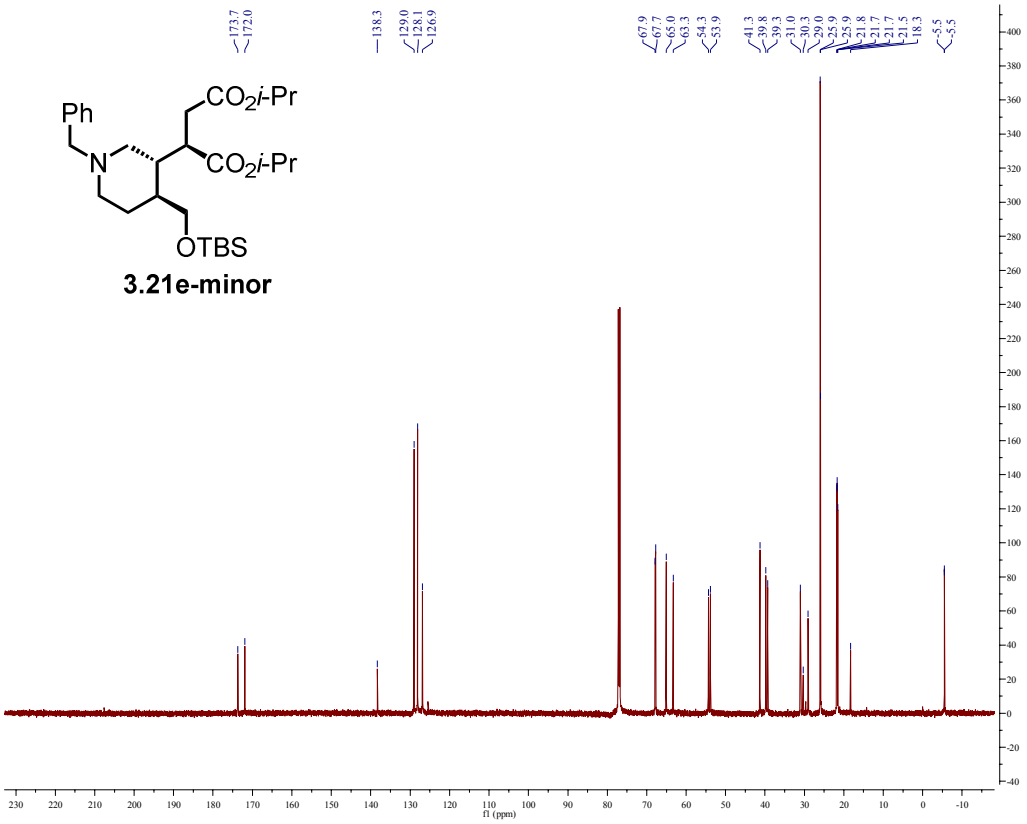
f1 (ppm)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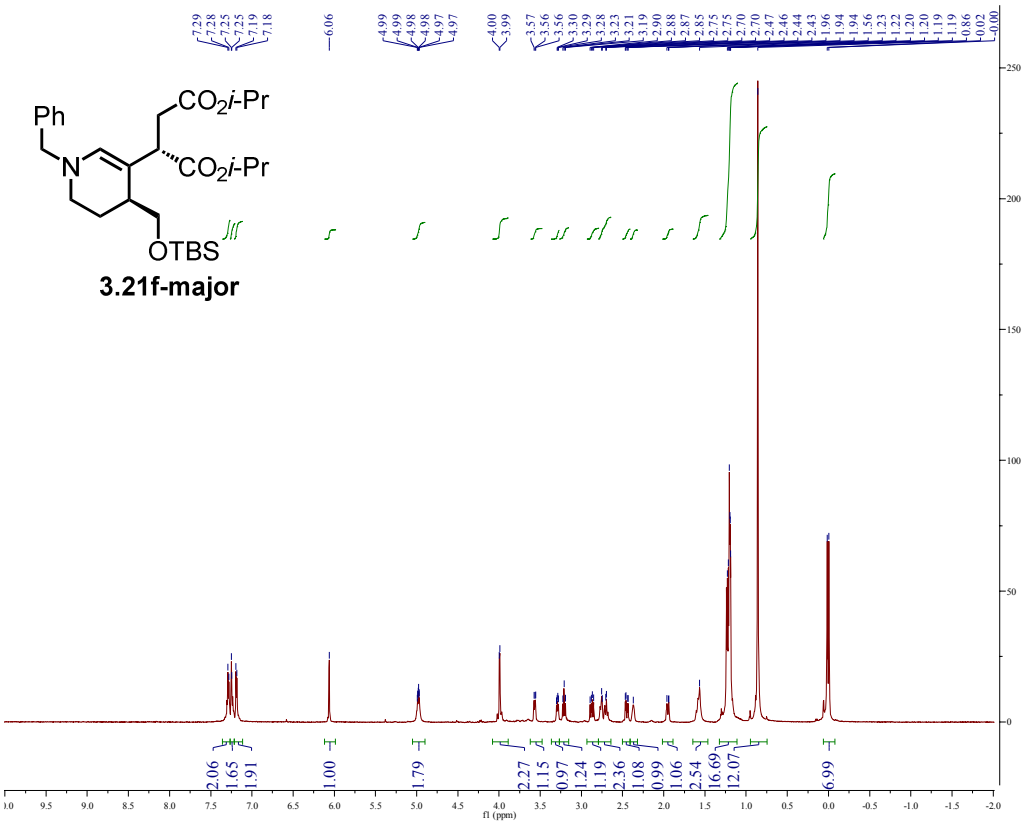
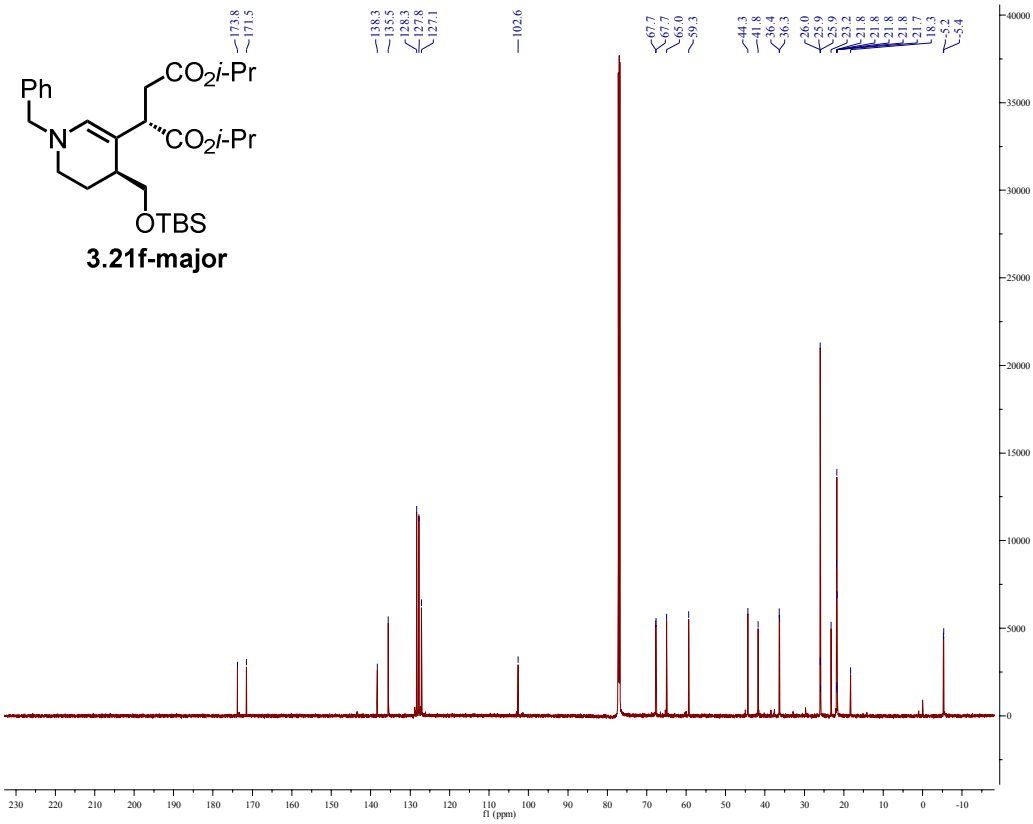
CO2i-Pr
CO2i-Pr
OTBS
3.21e-minor
f1 (ppm)



3.21f-major



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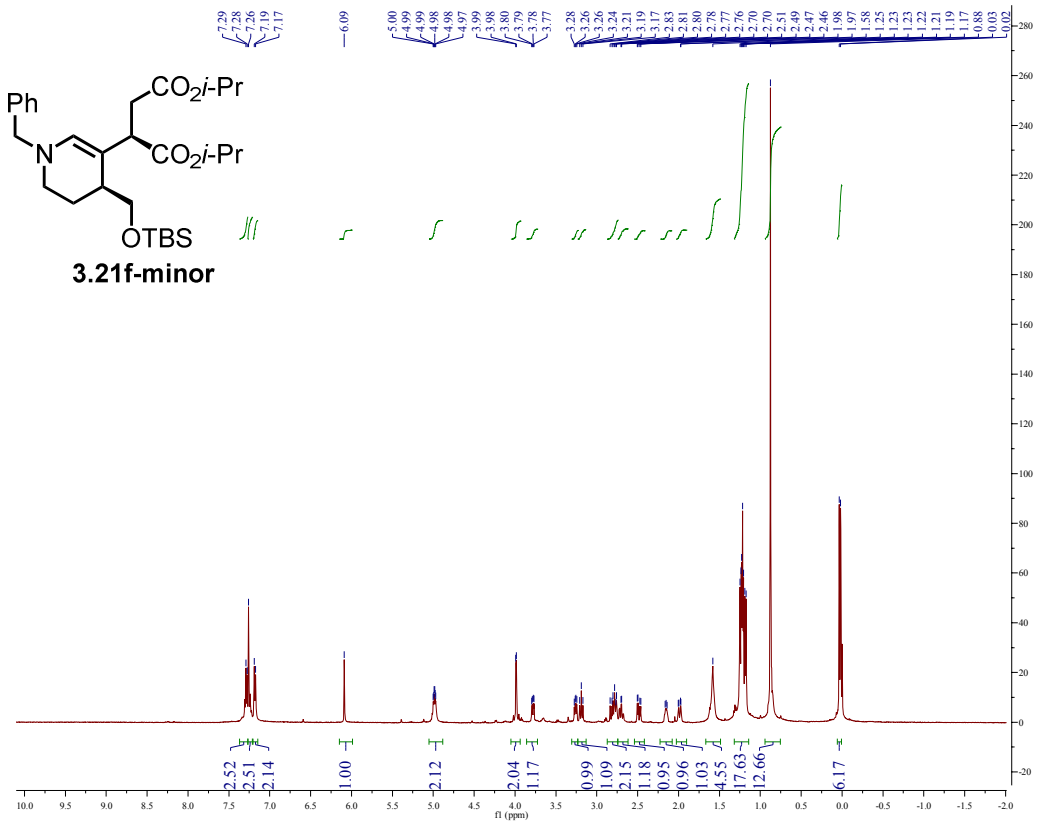
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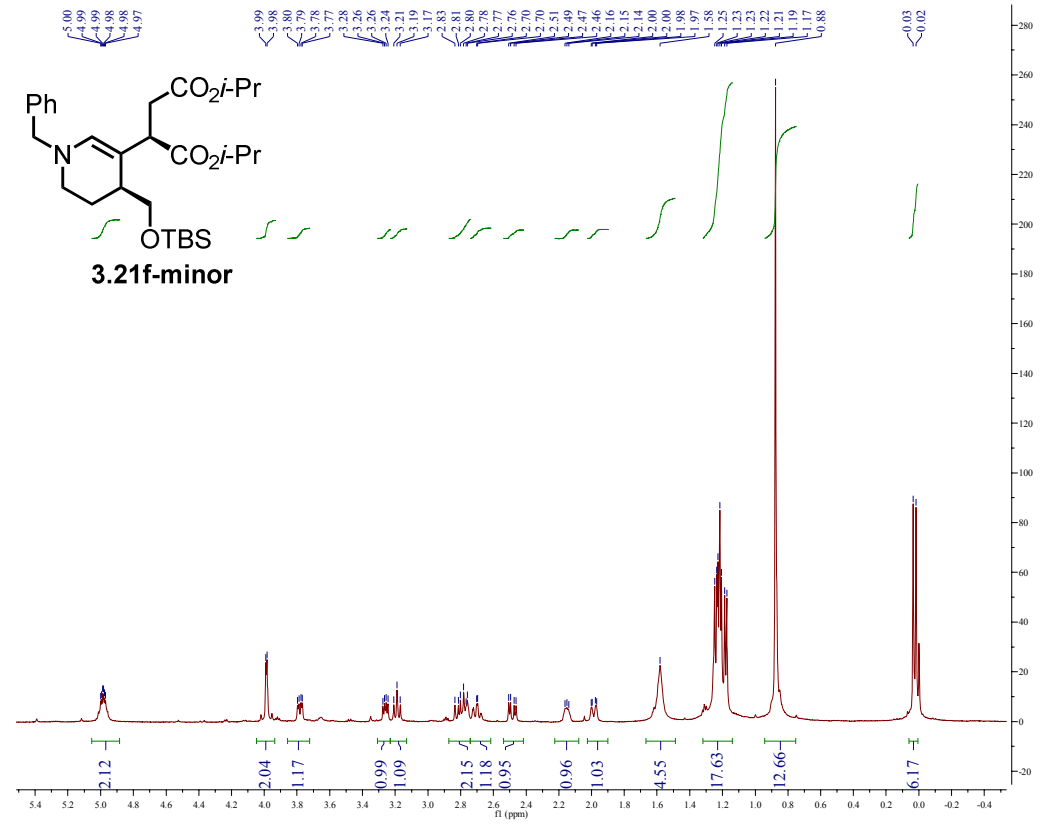
CO2i-Pr
CO2i-Pr
OTBS
3.21f-minor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CO2i-Pr
CO2i-Pr
OTBS
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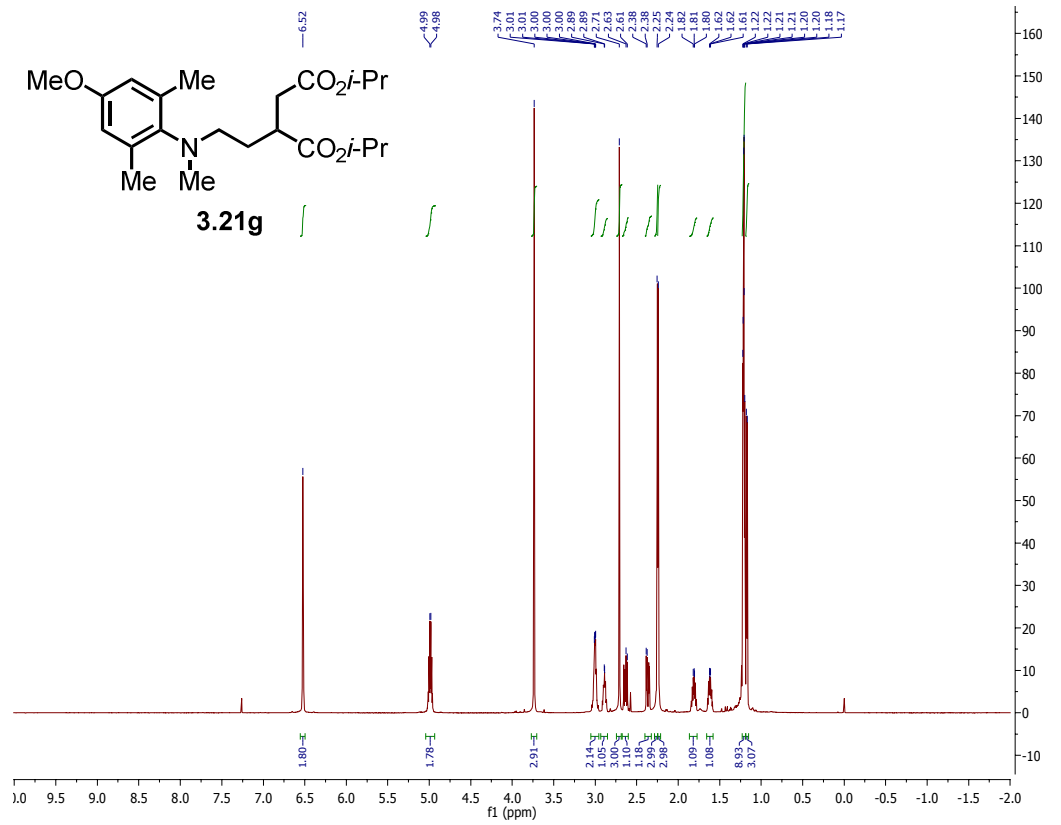
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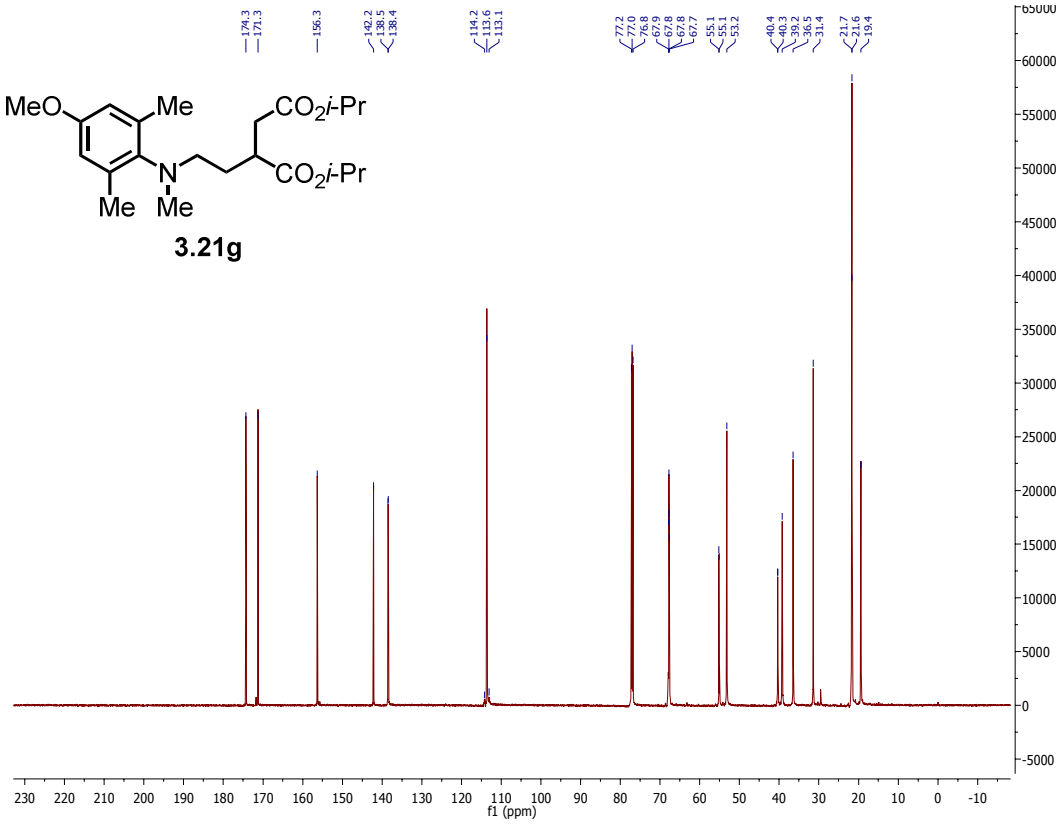
Me
CO2i-Pr
N
CO2i-Pr
Me
Me
3.21g
f1 (ppm)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Me
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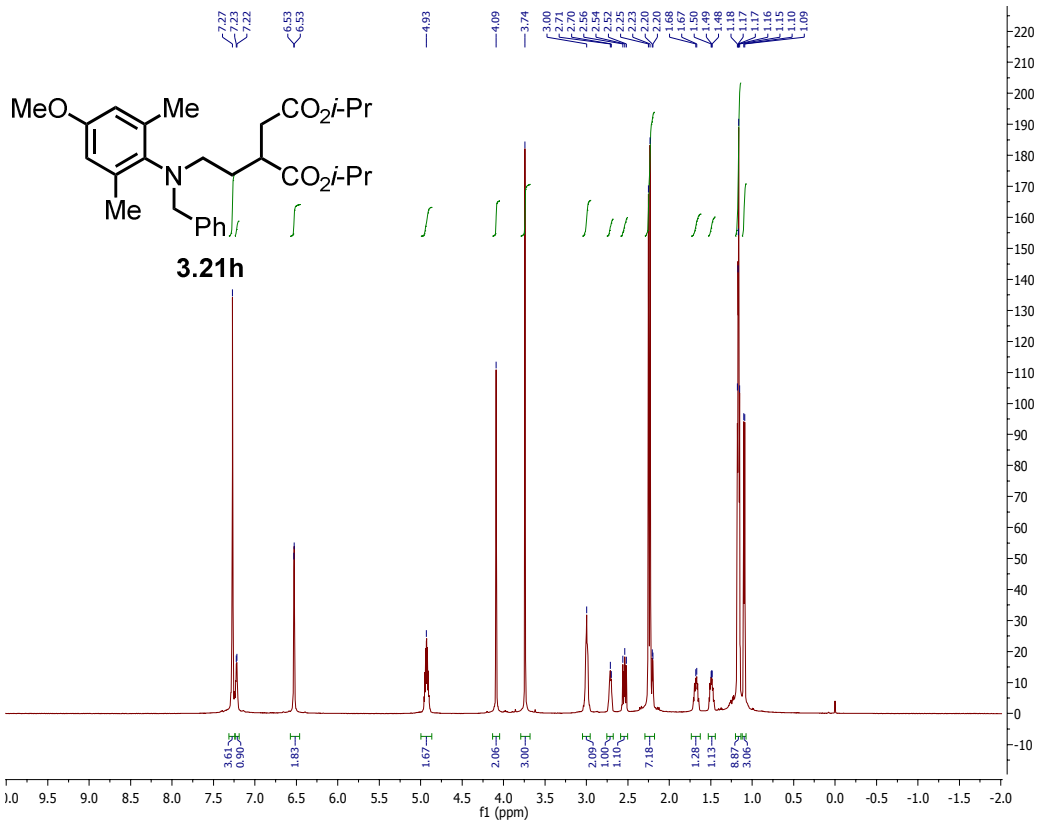
N
CO2i-Pr
Me
Me
3.21g
f1 (ppm)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Me
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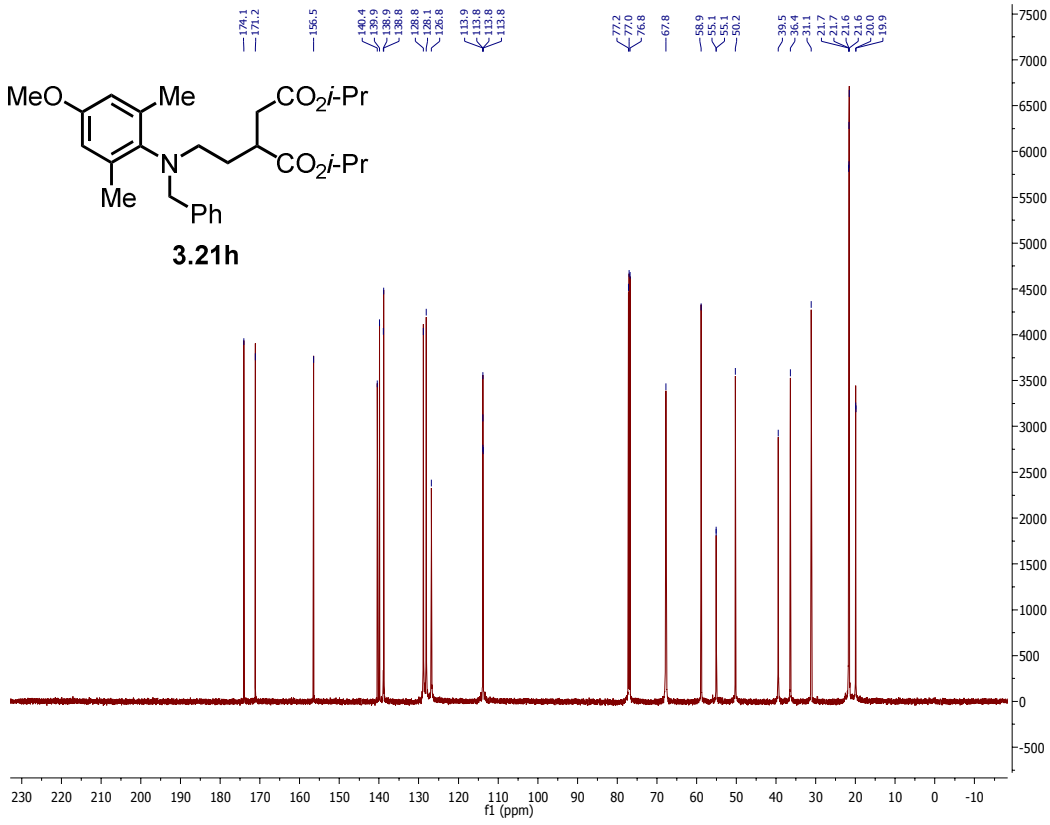
N
CO2i-Pr
Me
Ph
3.21h
f1 (ppm)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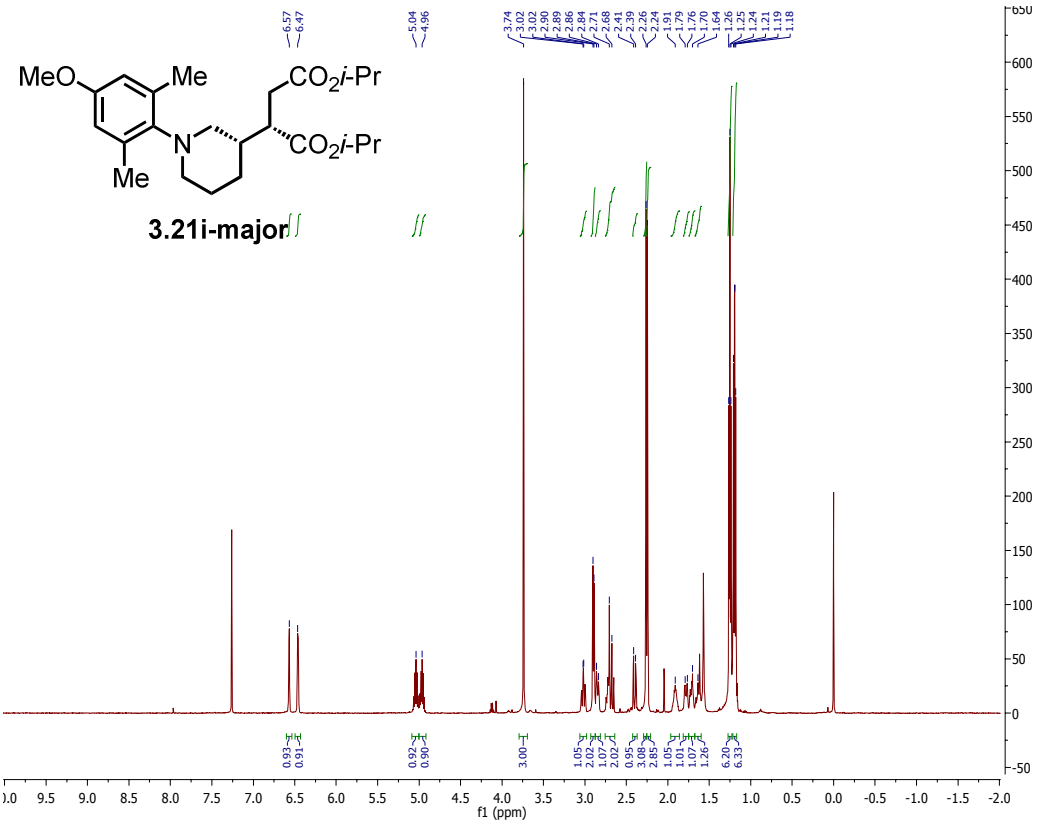
f1 (ppm)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CO2i-Pr
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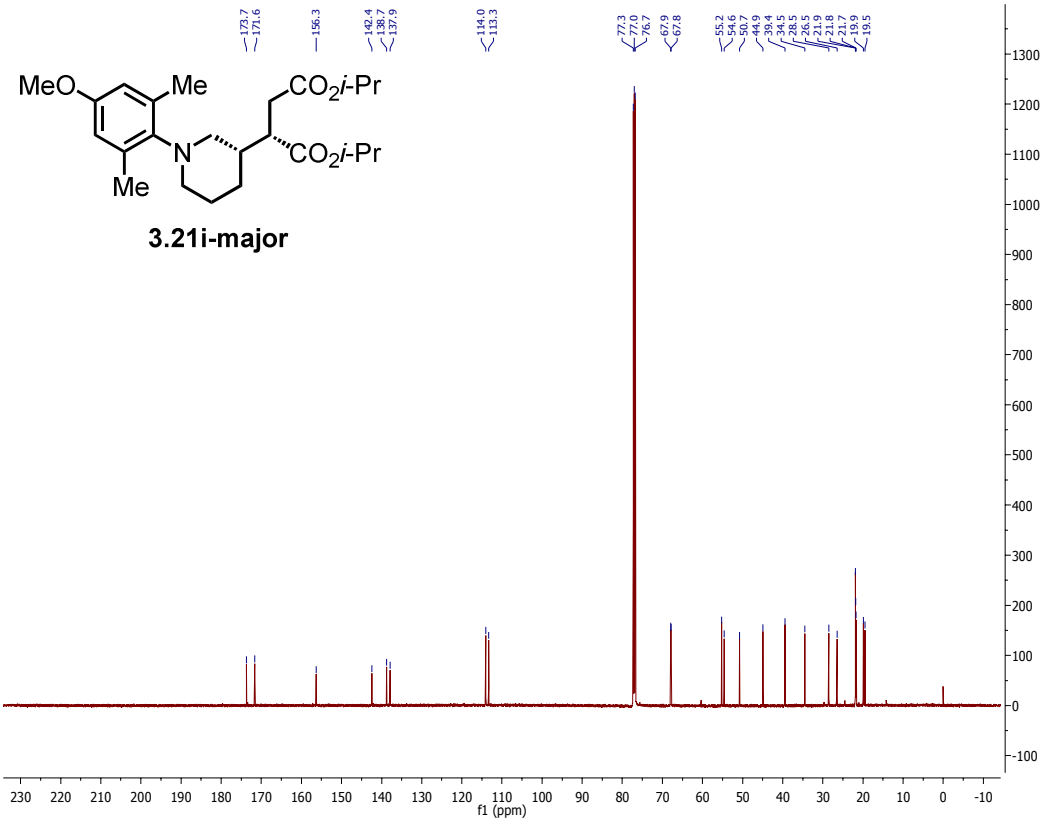
3.21i-major
f1 (ppm)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CO2i-Pr
CO2i-Pr
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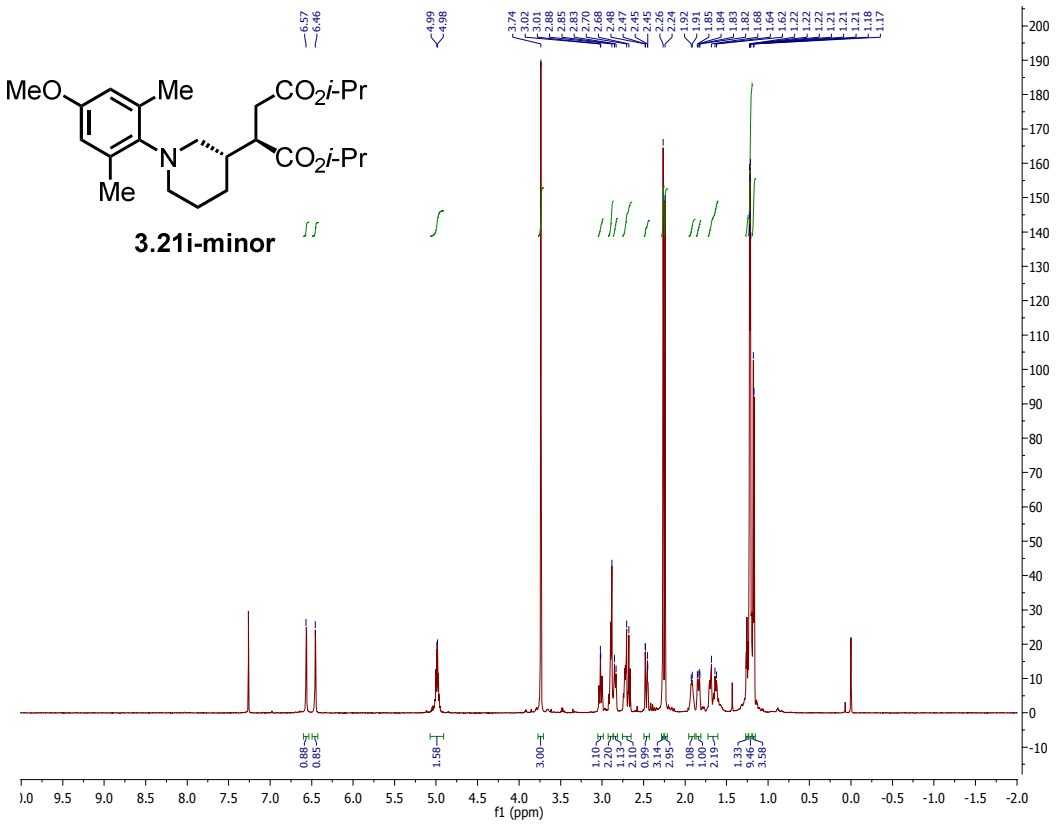
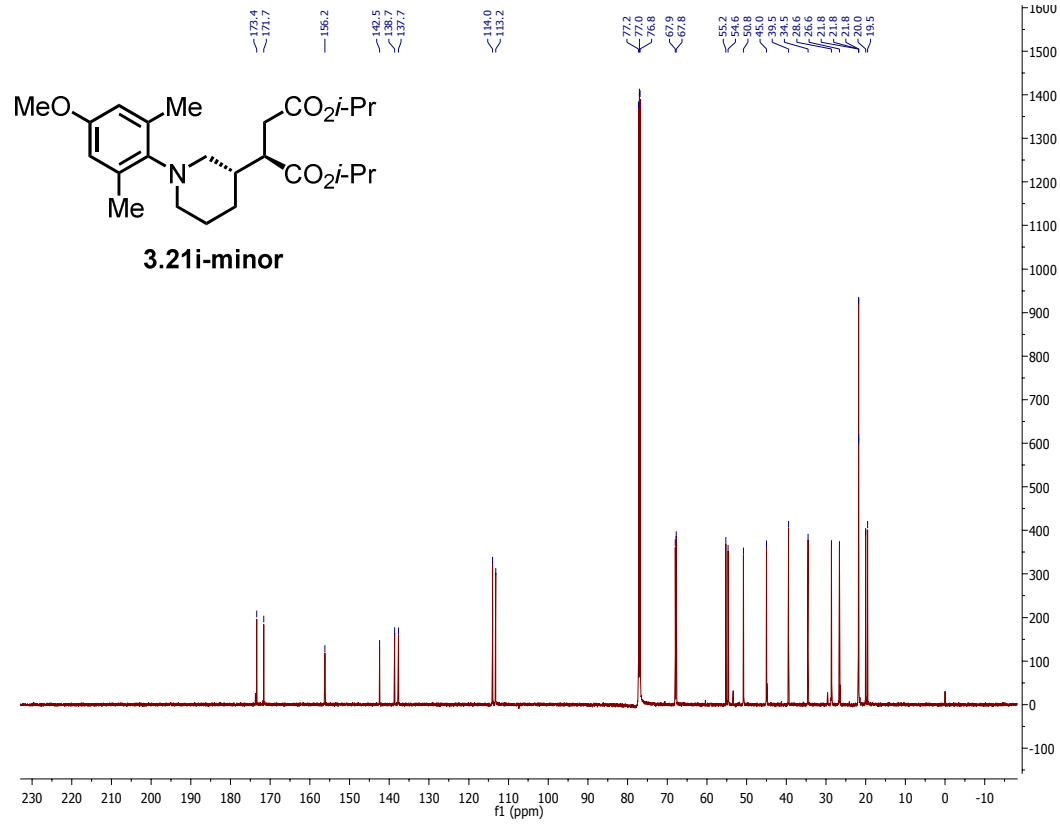
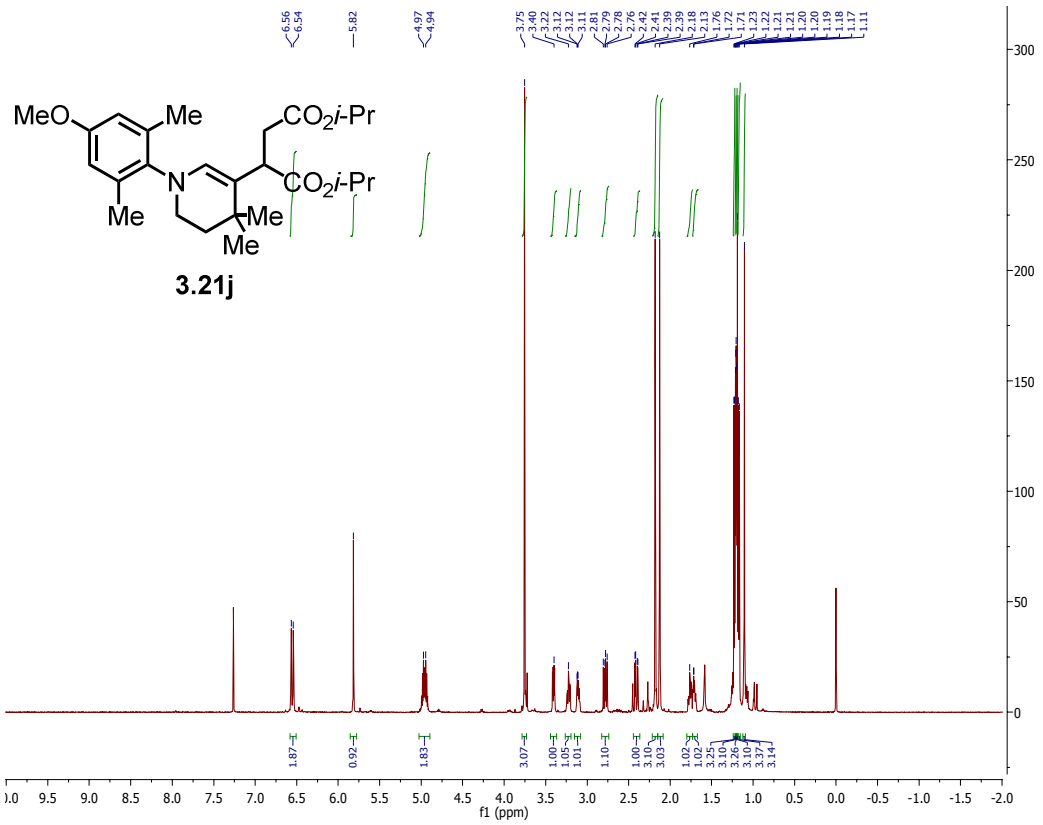
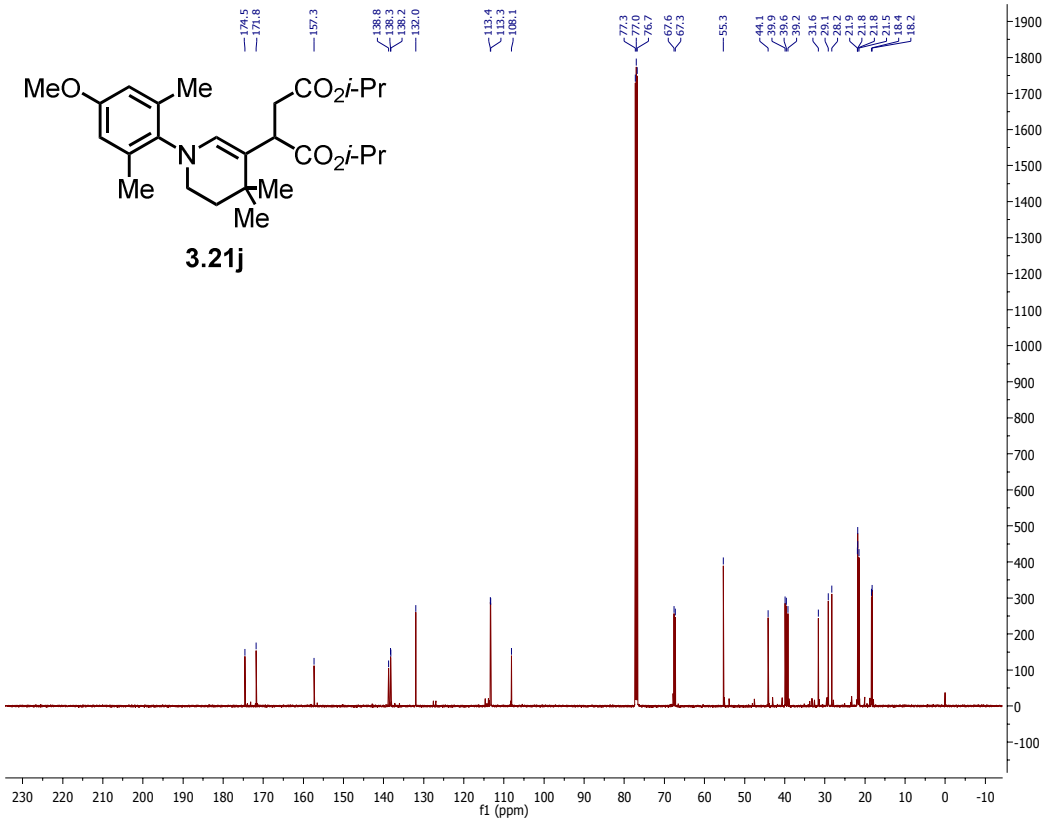
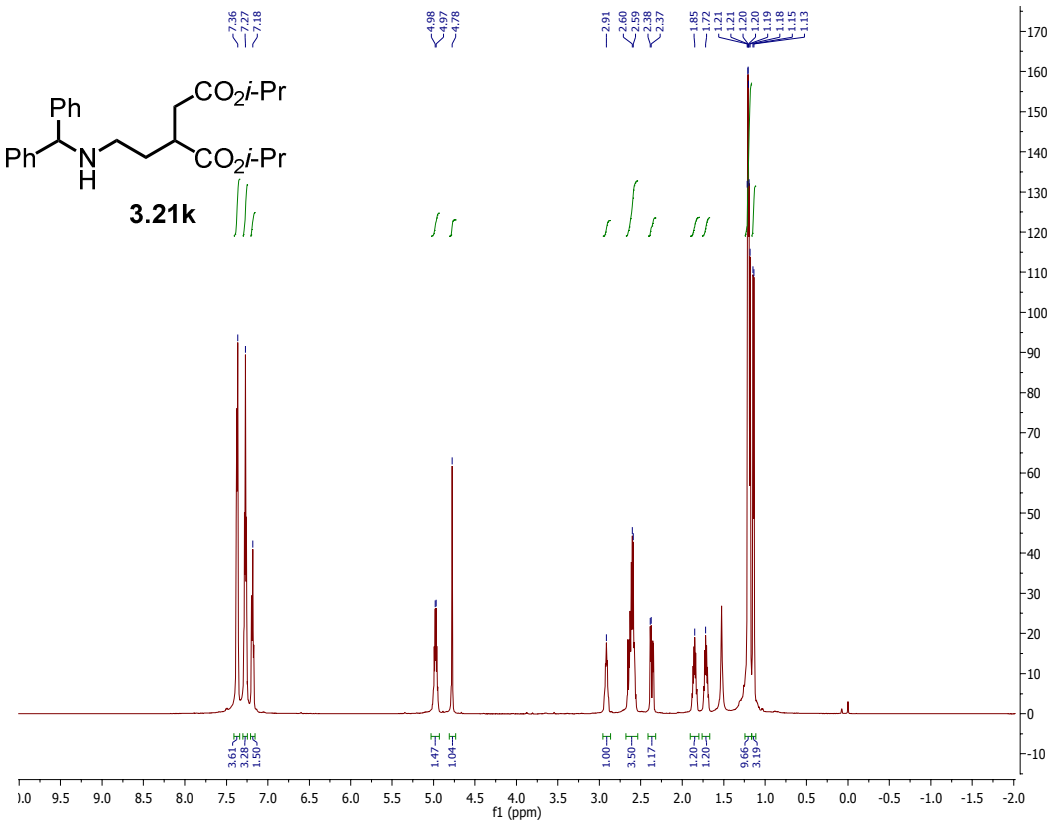
f1 (ppm)

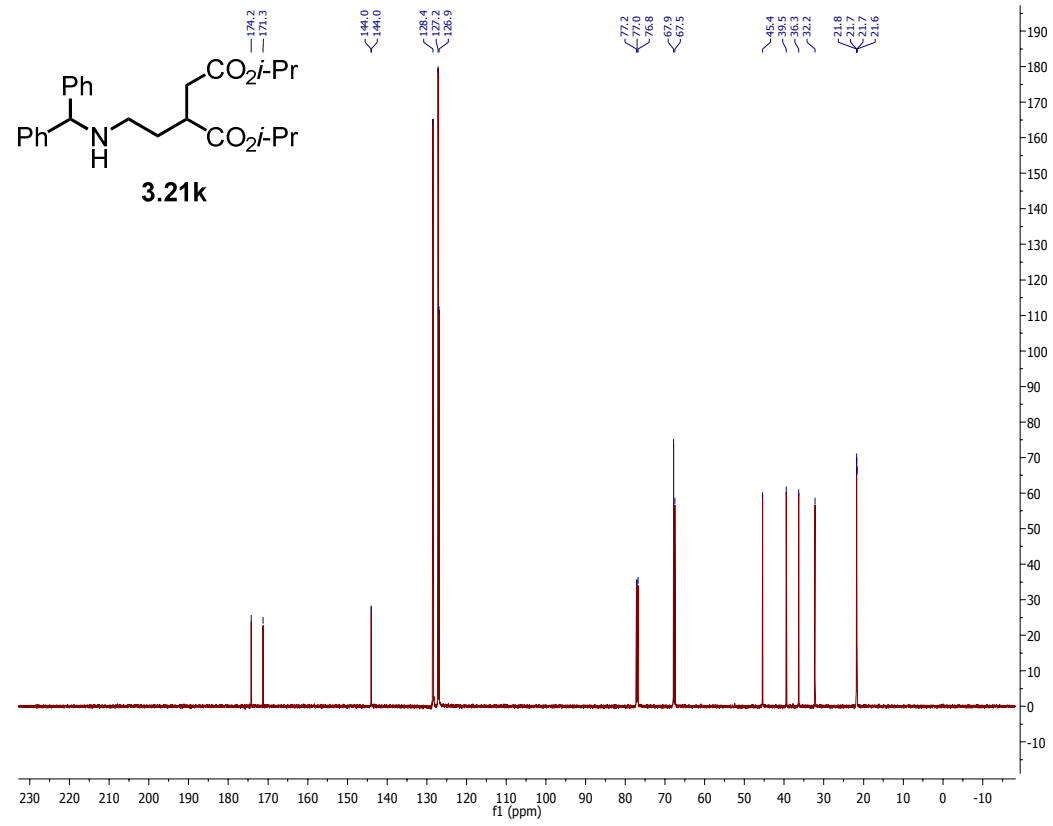

MeO
Me
CO2i-Pr
N
CO2i-Pr
Me
3.21i-minor
f1 (ppm)

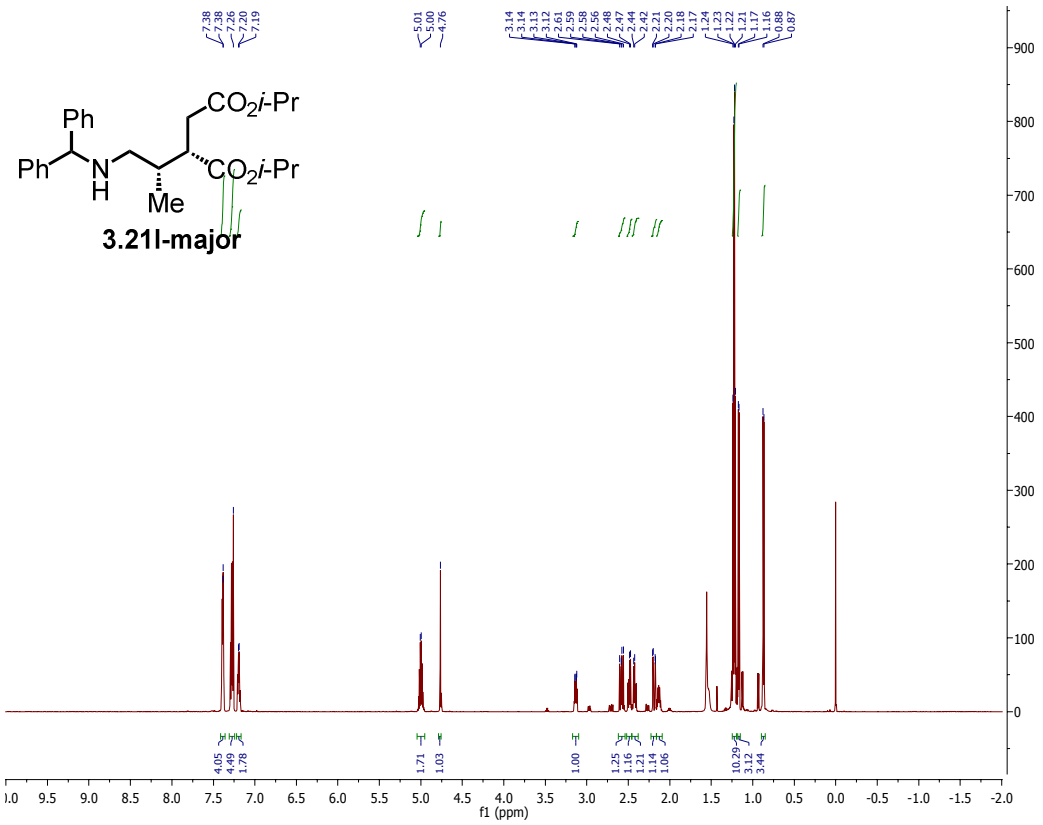

MeO
Me
CO2i-Pr
N
CO2i-Pr
Me
3.21i-minor
f1 (ppm)

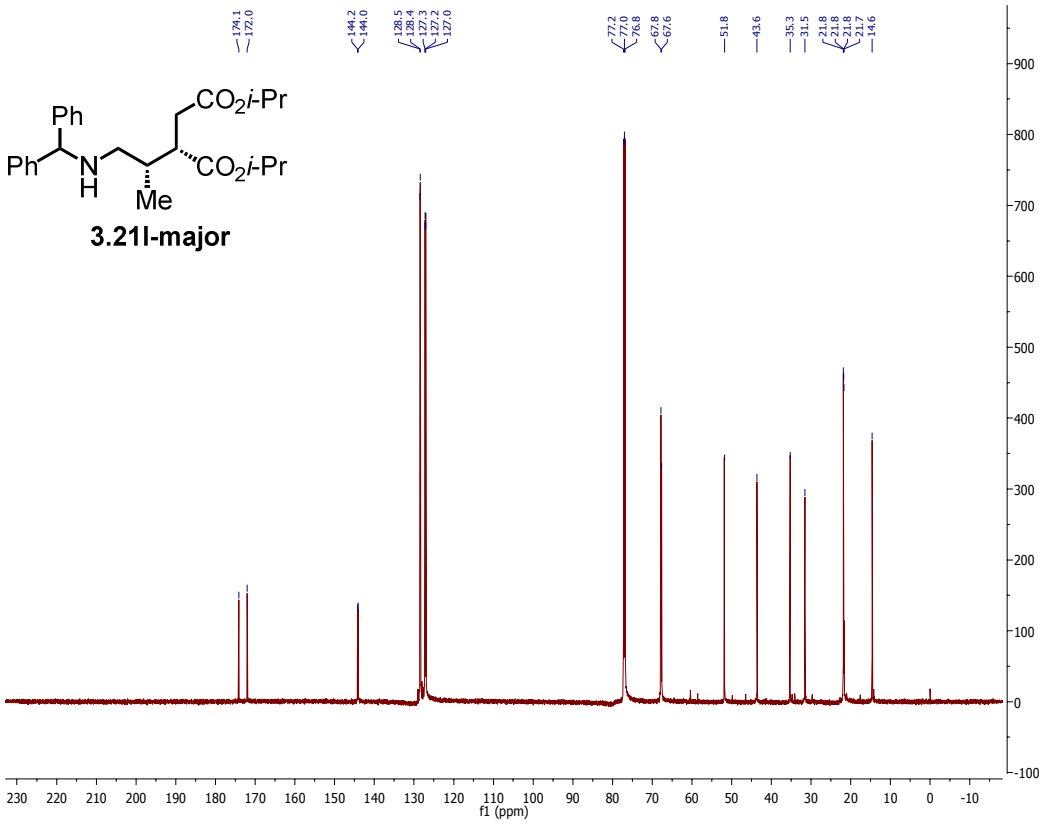

MeO
Me
CO2i-Pr
N
CO2i-Pr
Me
Me
Me
3.21j
f1 (ppm)

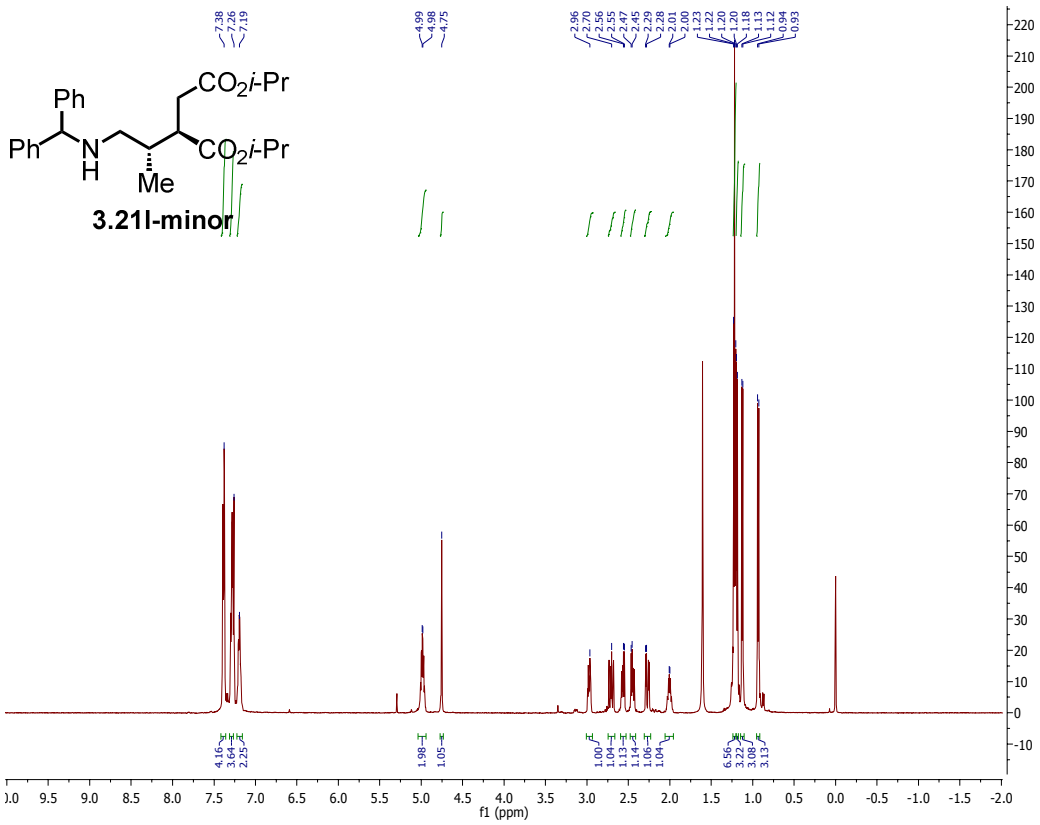

MeO
Me
CO2i-Pr
N
CO2i-Pr
Me
Me
Me
3.21j
f1 (ppm)

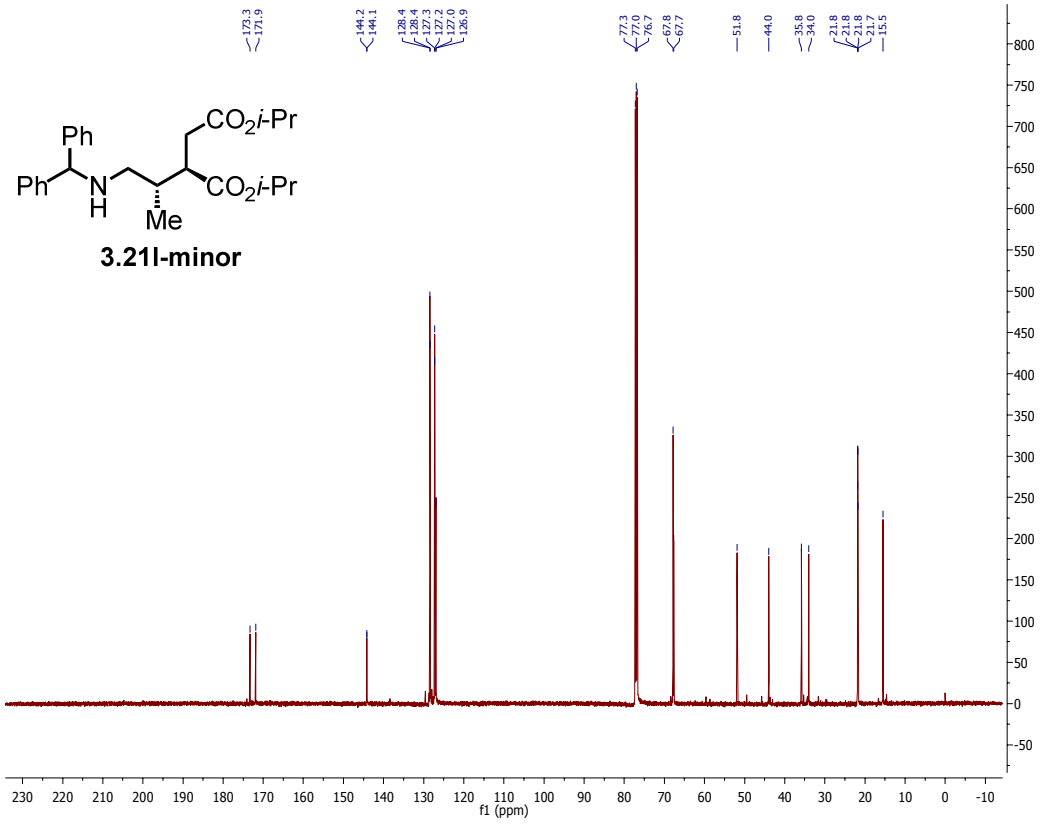

Ph
Ph
N
H
CO2i-Pr
CO2i-Pr
3.21k
7.36
7.27
7.18
4.98
4.97
4.78
2.91
2.60
2.59
2.38
2.37
1.85
1.72
1.21
1.21
1.20
1.20
1.19
1.18
1.15
1.13
3.61
3.28
1.50
1.47
1.04
1.00
3.50
1.17
1.20
1.20
9.66
3.19
f1 (ppm)

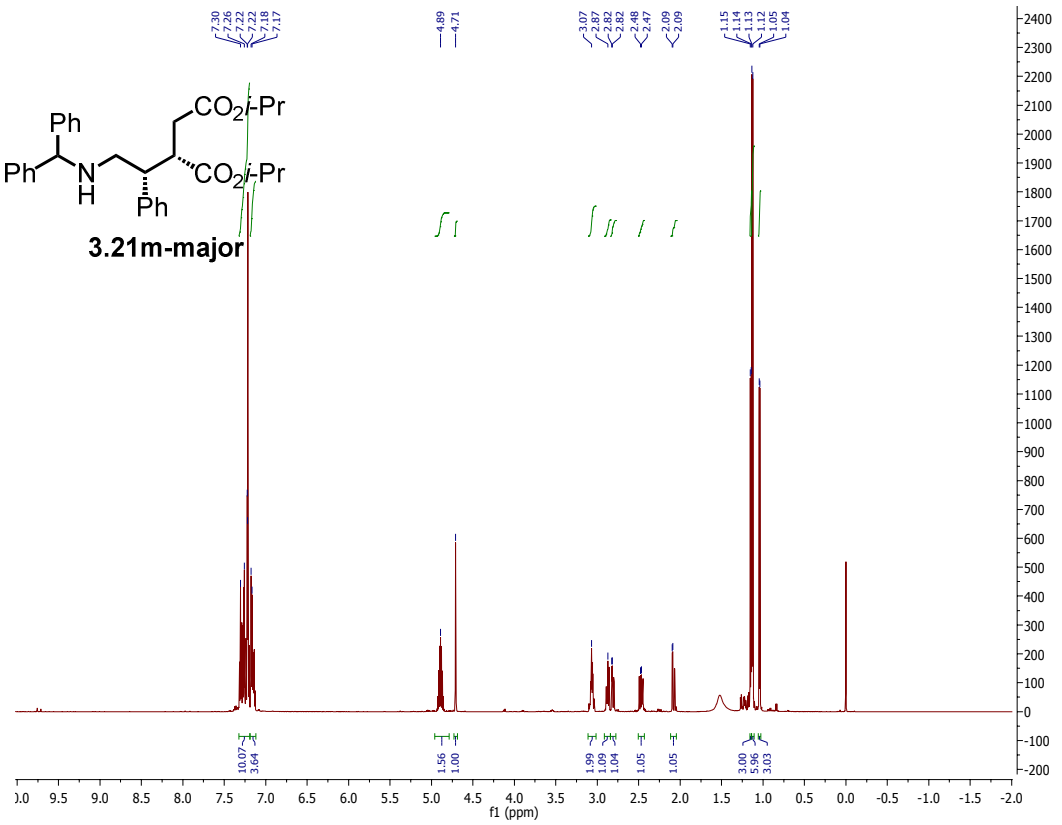

Ph
Ph
N
H
CO2i-Pr
CO2i-Pr
3.21k
174.2
171.3
144.0
144.0
128.4
127.2
126.9
77.2
77.0
76.8
67.9
67.5
45.4
39.5
36.3
32.2
21.8
21.7
21.7
21.6
f1 (ppm)

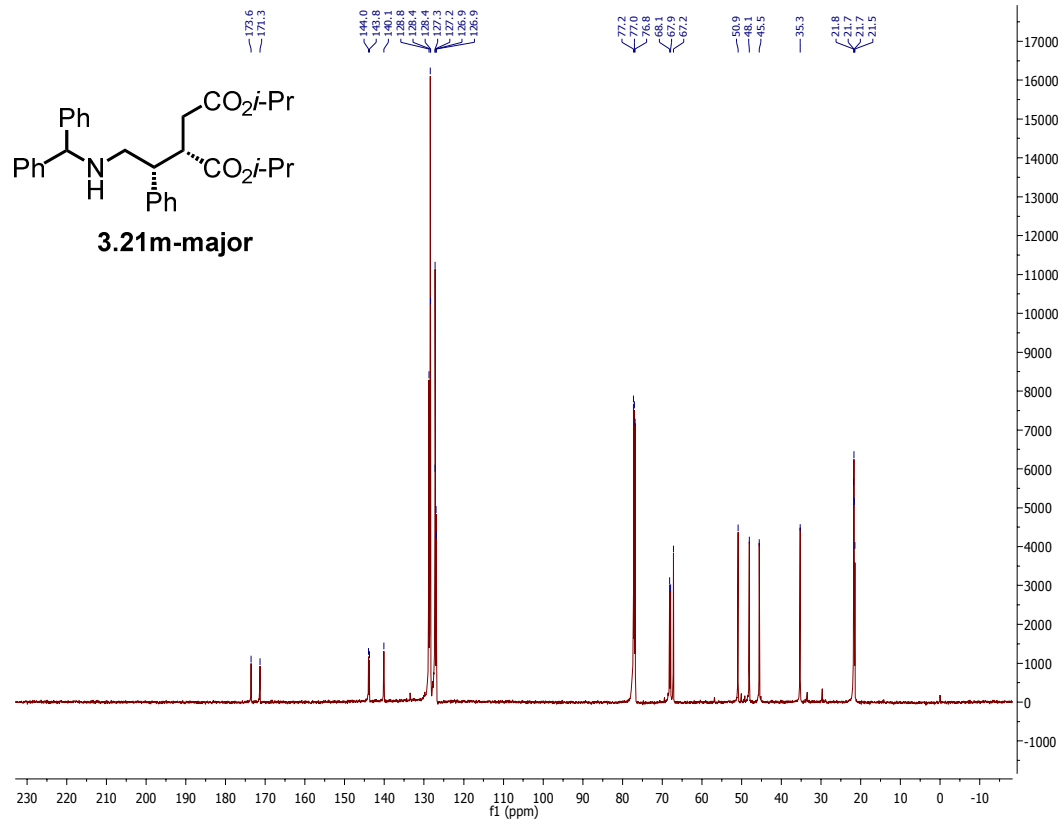

Ph
Ph
N
H
Me
CO2i-Pr
CO2i-Pr
3.21l-major
f1 (ppm)

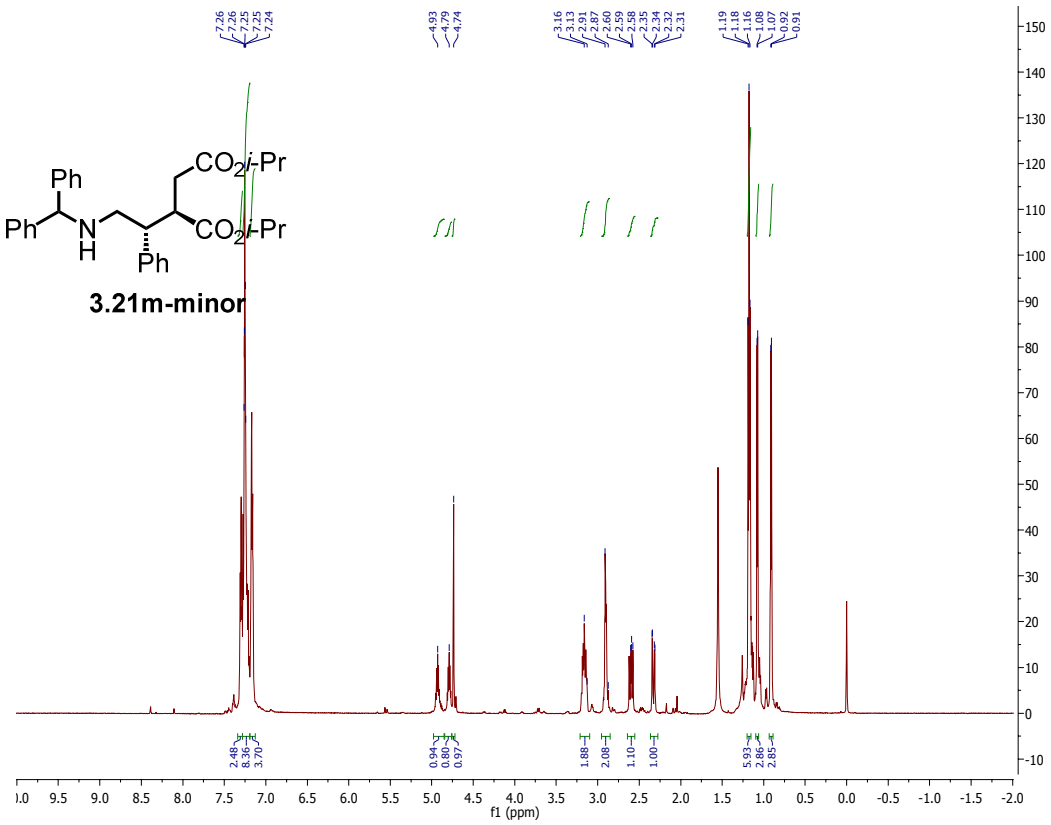

Ph
Ph
N
H
Me
CO2i-Pr
CO2i-Pr
3.21l-major
f1 (ppm)

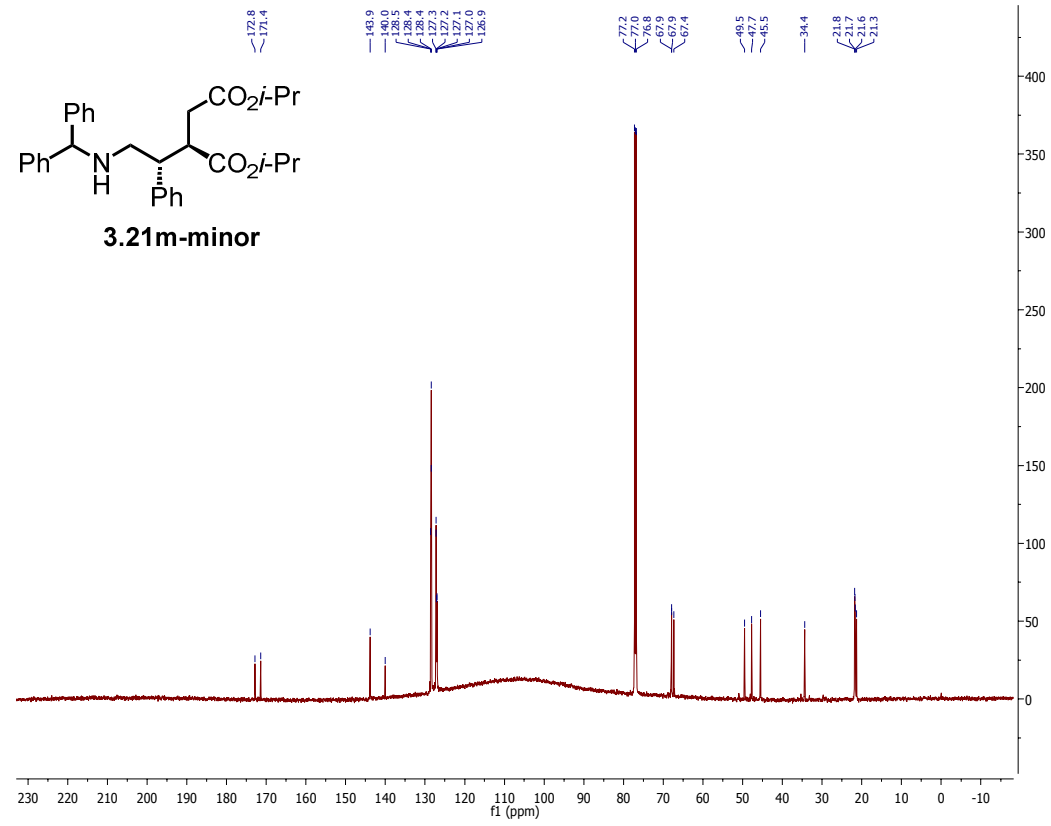

Ph
Ph
N
H
Me
CO2i-Pr
CO2i-Pr
3.21l-minor
f1 (ppm)

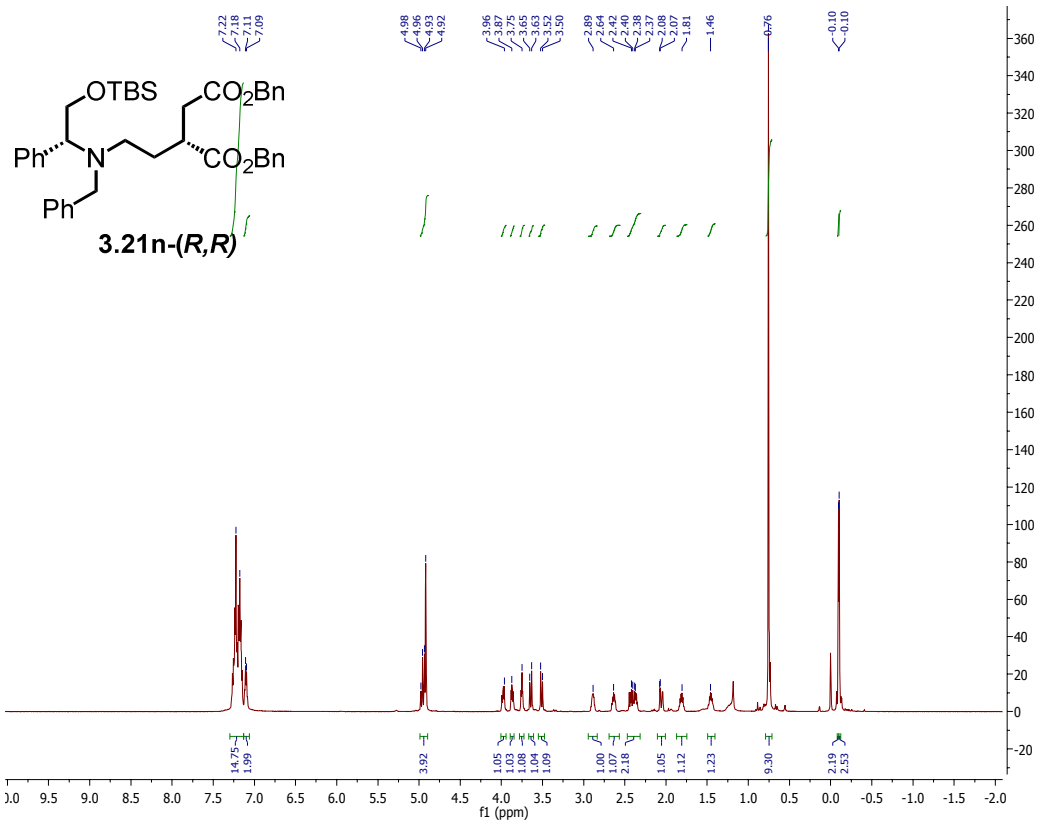

Ph
Ph
N
H
Me
CO2i-Pr
CO2i-Pr
3.21l-minor
f1 (ppm)

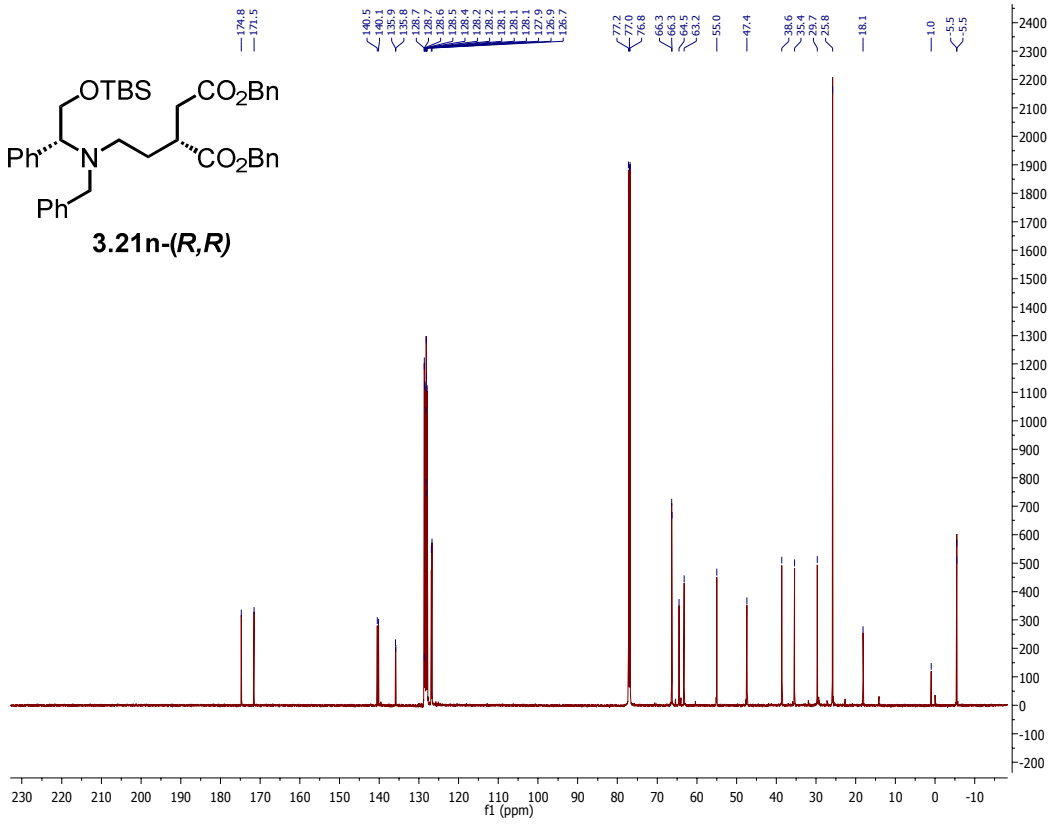

Ph
Ph
N
H
CO2i-Pr
CO2i-Pr
Ph
3.21m-major
f1 (ppm)

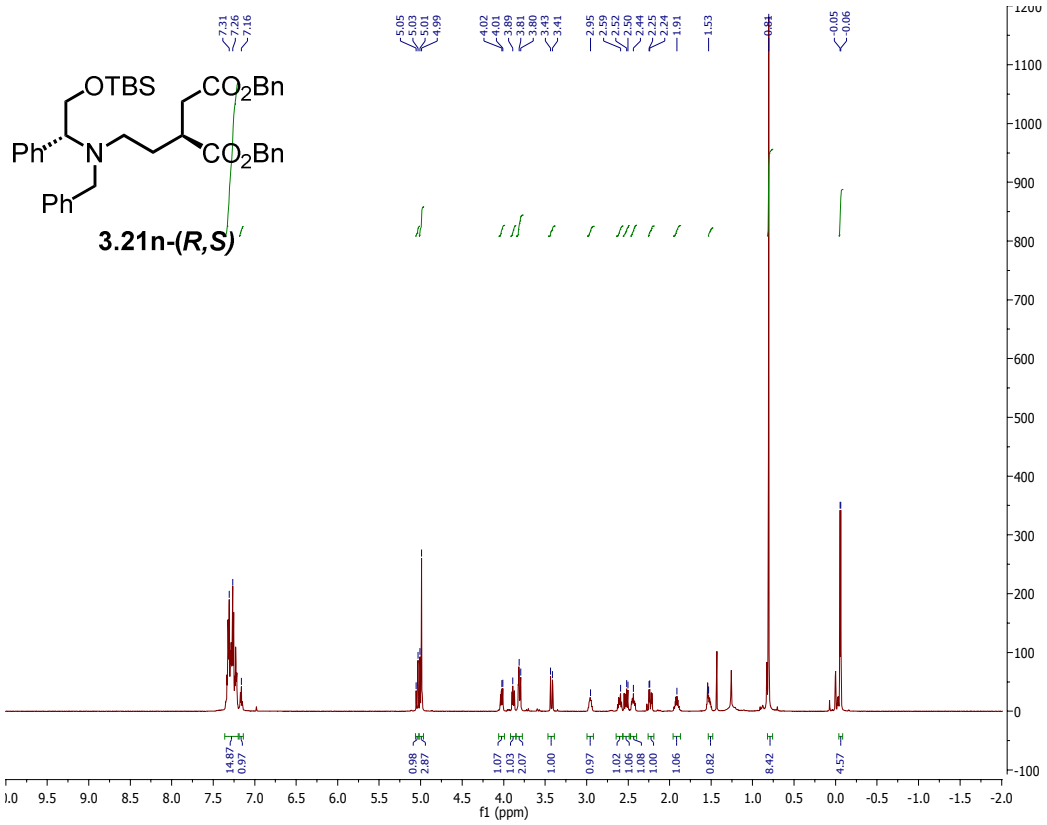

Ph
Ph
N
H
CO2i-Pr
CO2i-Pr
Ph
3.21m-major
f1 (ppm)

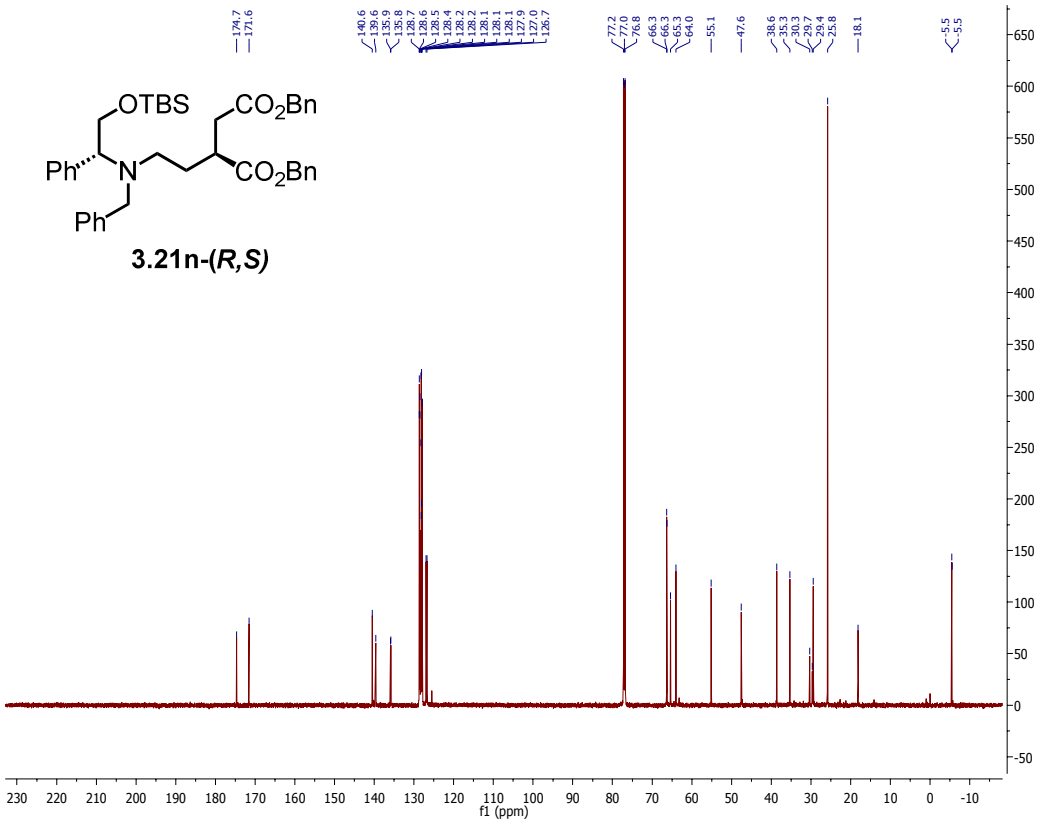

Ph
Ph
N
H
Ph
CO2i-Pr
CO2i-Pr
3.21m-minor
f1 (ppm)

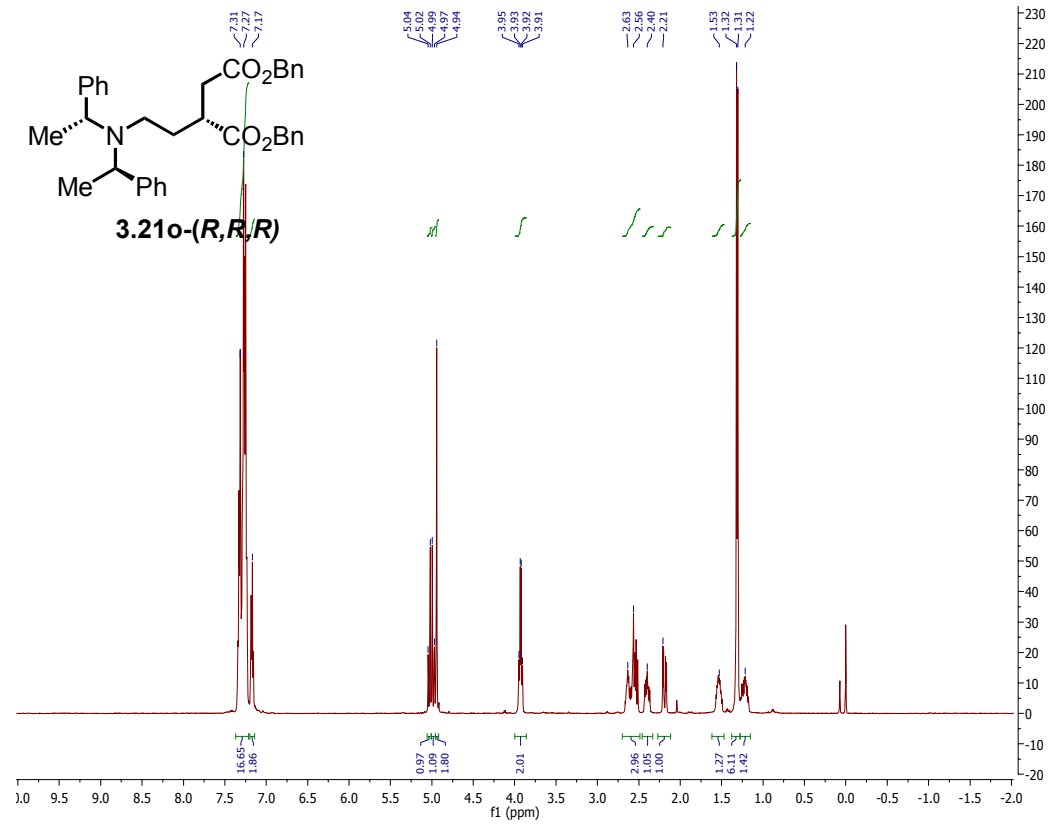

Ph
Ph
N
H
Ph
CO2i-Pr
CO2i-Pr
3.21m-minor
f1 (ppm)


OTBS
CO2Bn
Ph
N
CO2Bn
Ph
3.21n-(R,R)
f1 (ppm)

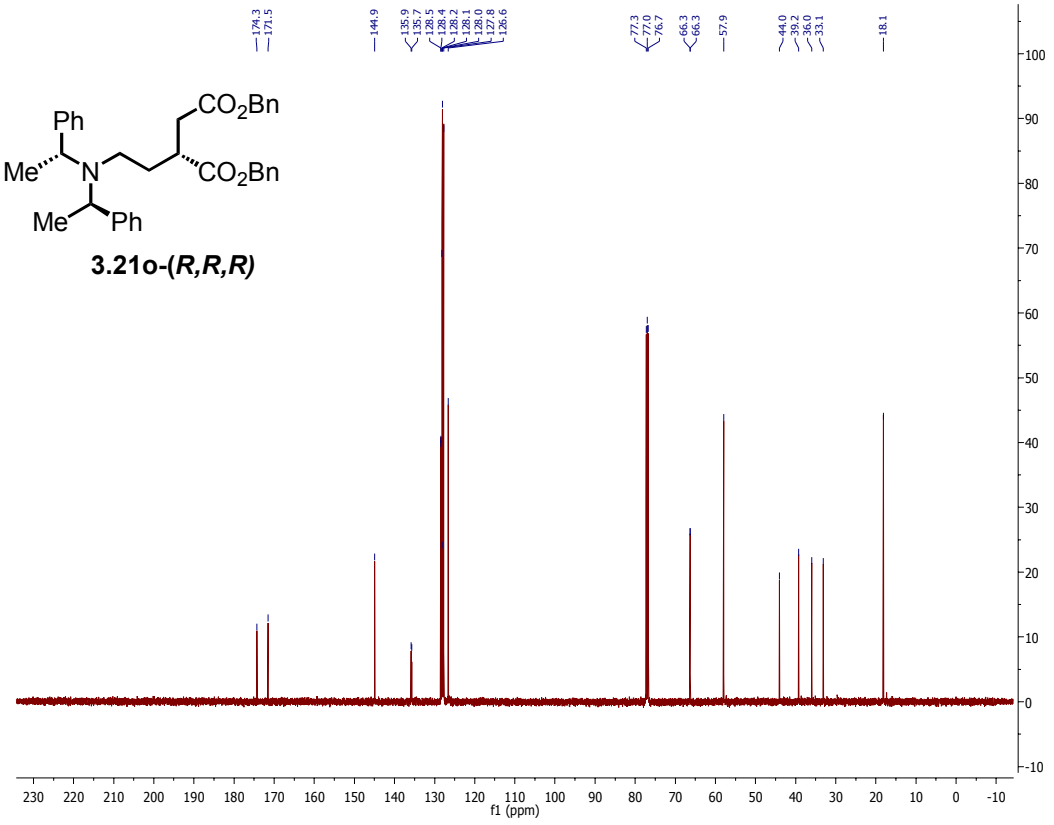

OTBS
CO2Bn
Ph
N
CO2Bn
Ph
3.21n-(R,R)
f1 (ppm)


OTBS
CO2Bn
Ph
N
CO2Bn
Ph
3.21n-(R,S)
f1 (ppm)

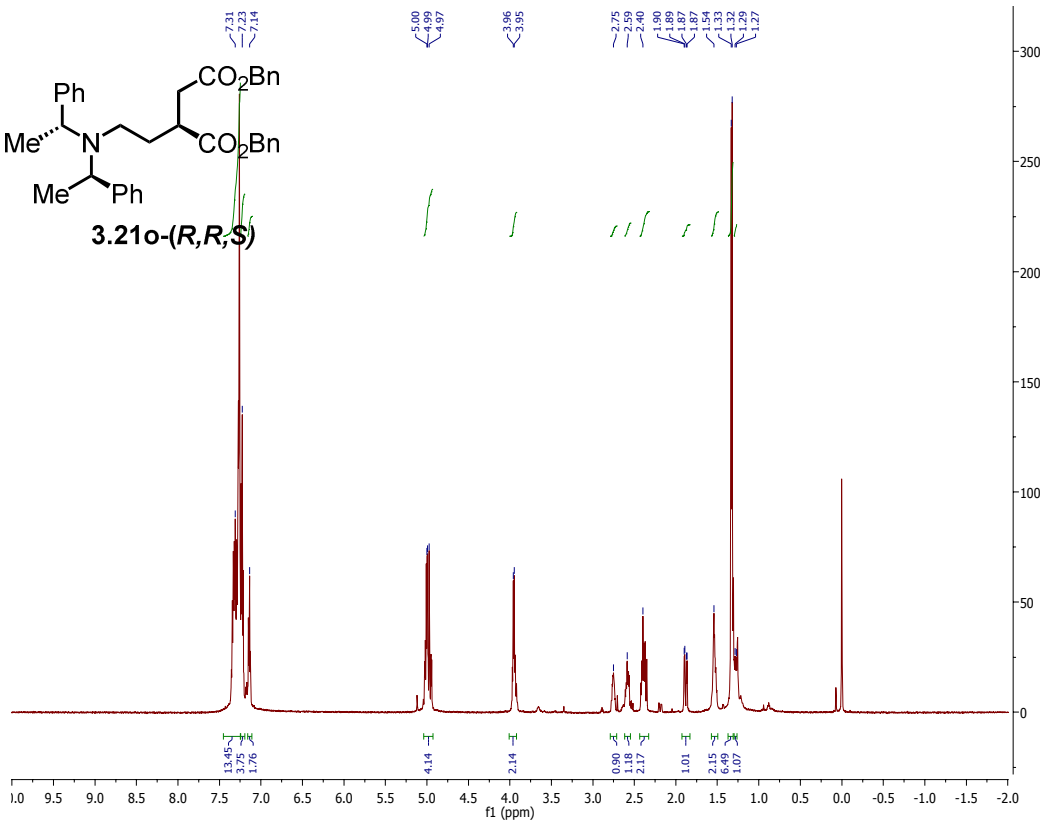

OTBS
CO2Bn
Ph
N
CO2Bn
Ph
3.21n-(R,S)
f1 (ppm)

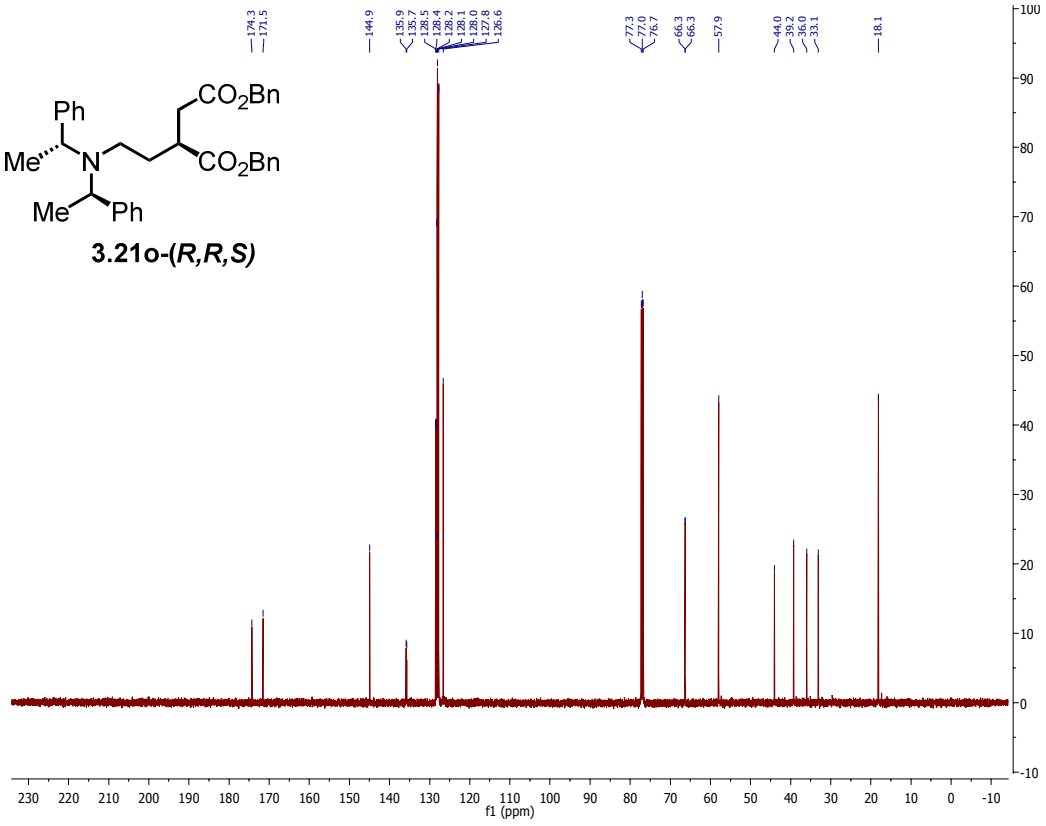


3.21o-(*R,R,R*)

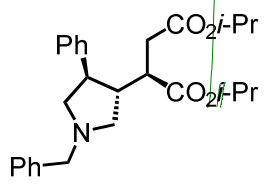


3.21o-(*R,R,R*)


Ph
Me
N
Me
Ph
CO2Bn
CO2Bn
3.21o-(R,R,S)
f1 (ppm)

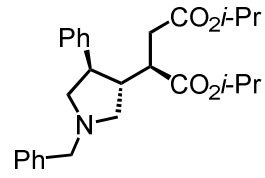

Ph
Me
N
Me
Ph
CO2Bn
CO2Bn
3.21o-(R,R,S)
f1 (ppm)

^{1}H NMR (500 MHz, $CDCl_3$)

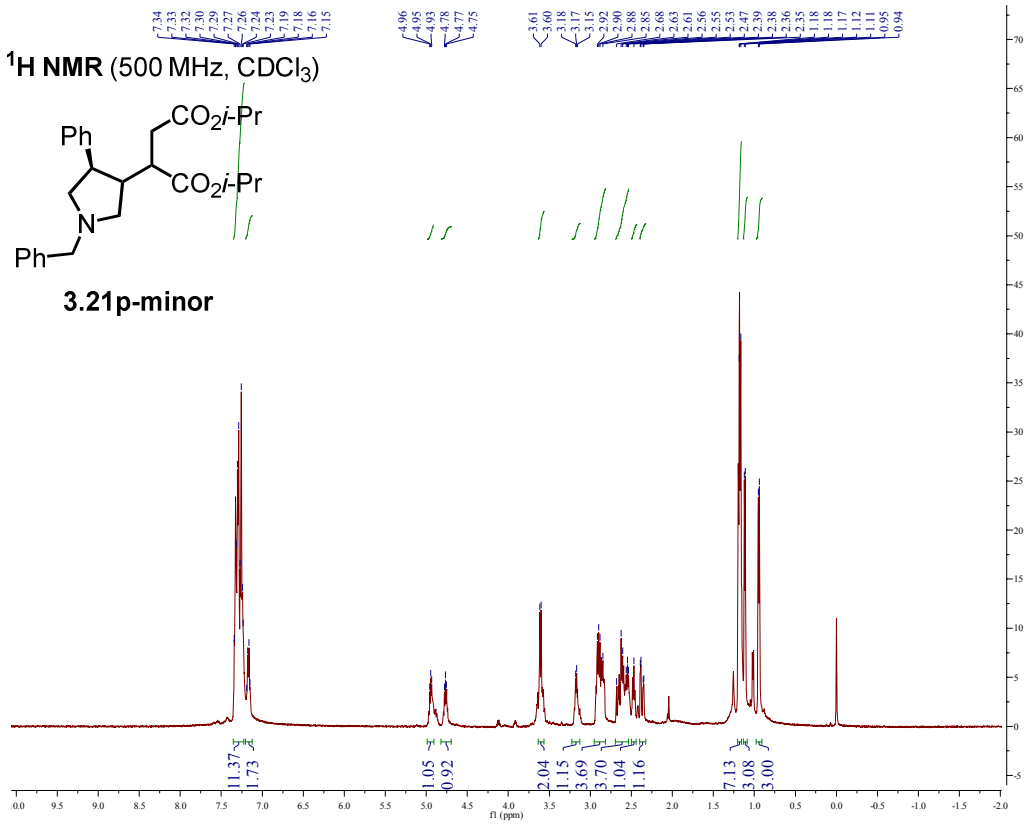


3.21p-(*R,R,R*)

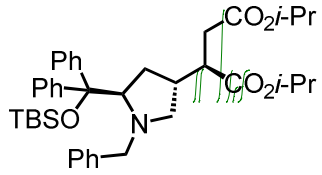
^{13}C NMR (151 MHz, $CDCl_3$)



3.21p-(*R,R,R*)

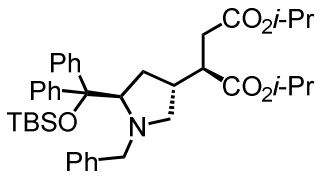

1H NMR (500 MHz, CDCl3)
CO2i-Pr
Ph
CO2i-Pr
N
Ph
3.21p-minor
f1 (ppm)

^{1}H NMR (600 MHz, $CDCl_3$)

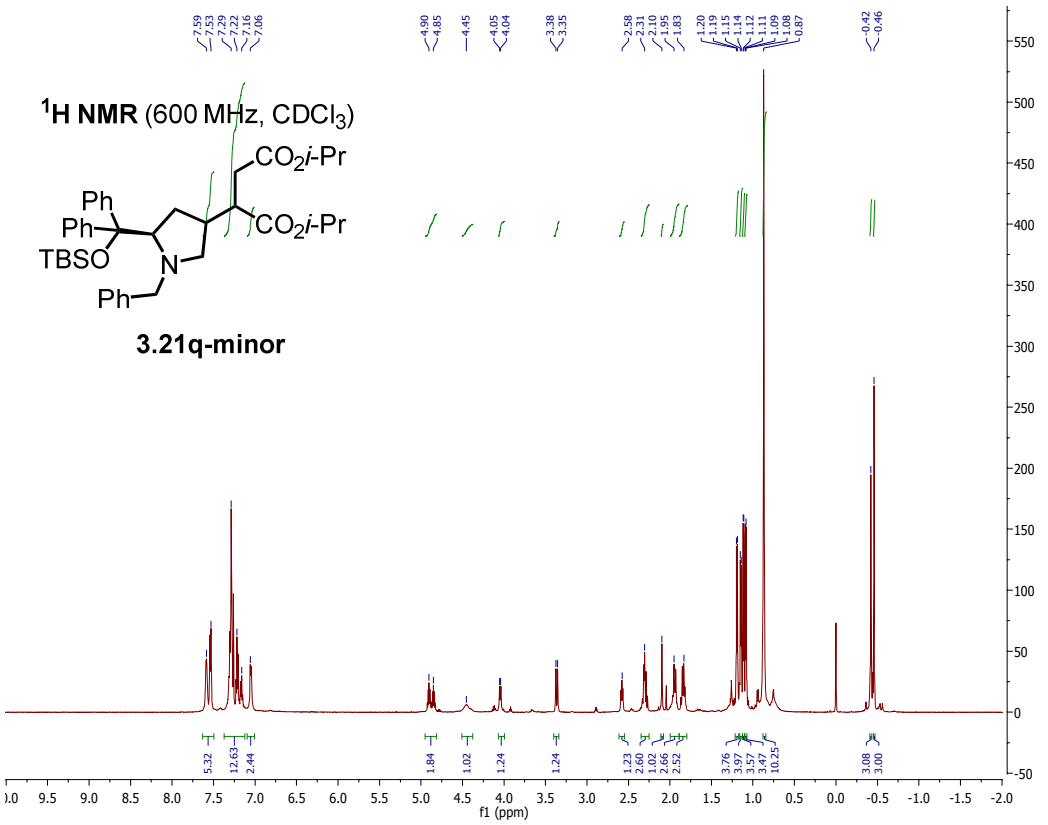


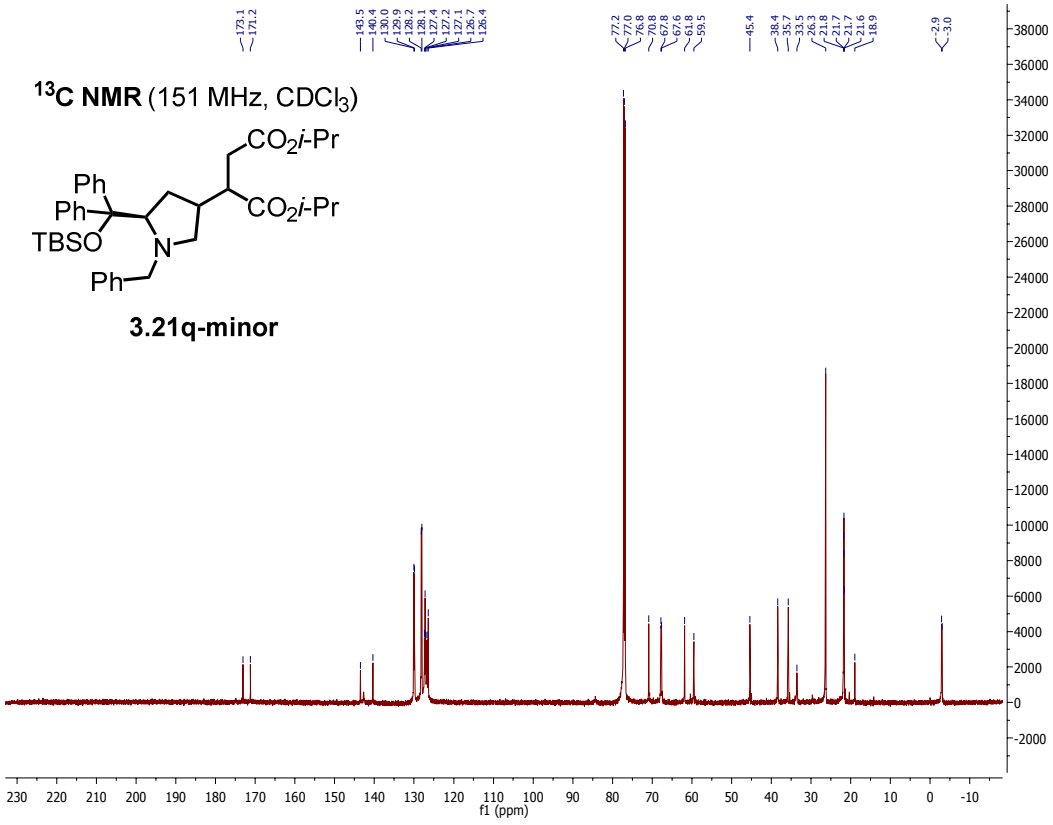
3.21q-(*R,R,R*)

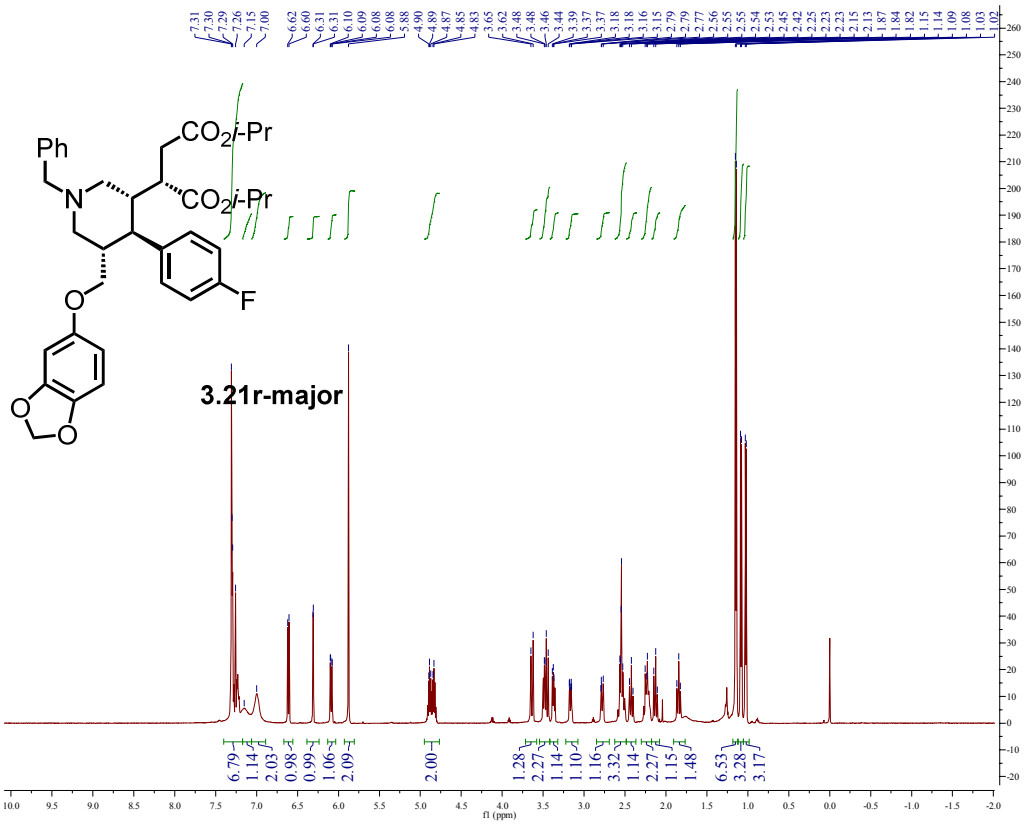
^{13}C NMR (151 MHz, $CDCl_3$)

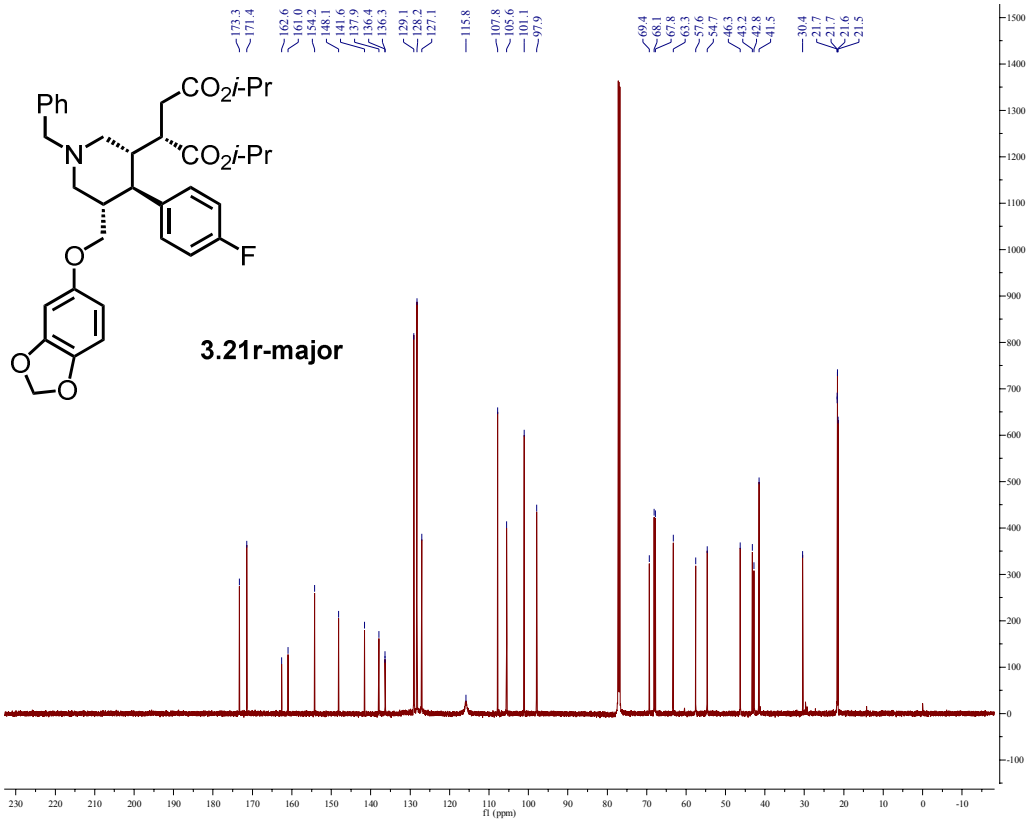


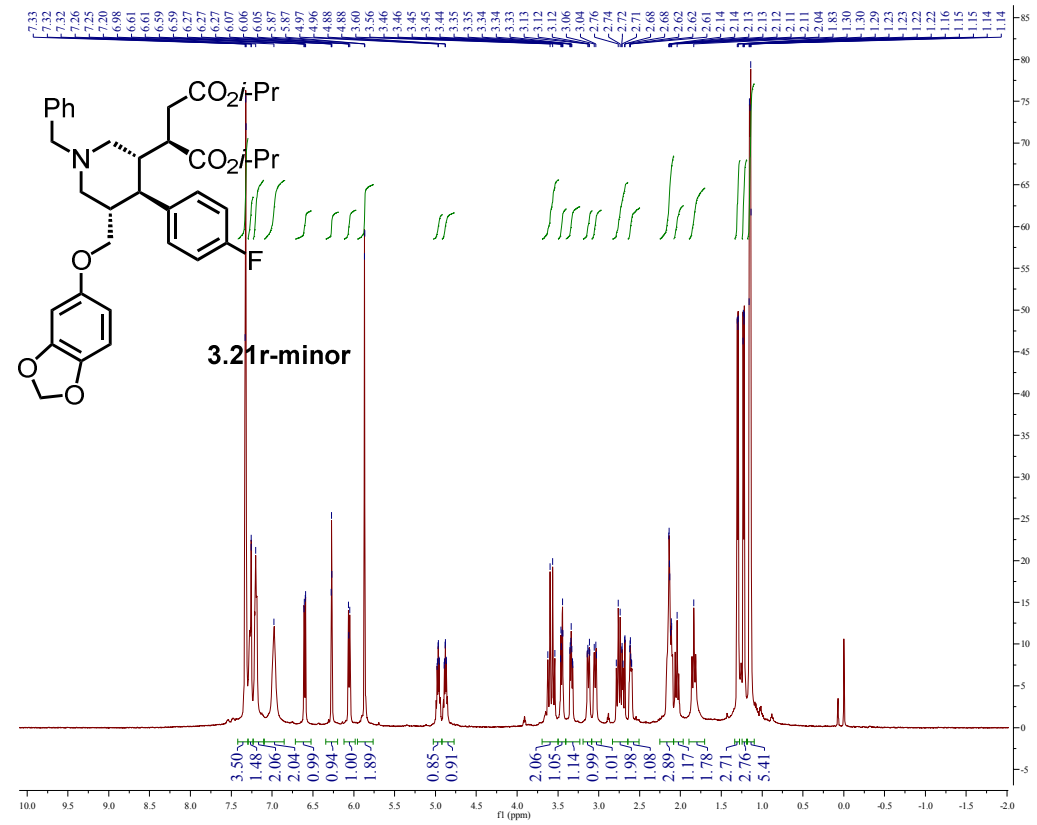
3.21q-(*R,R,R*)

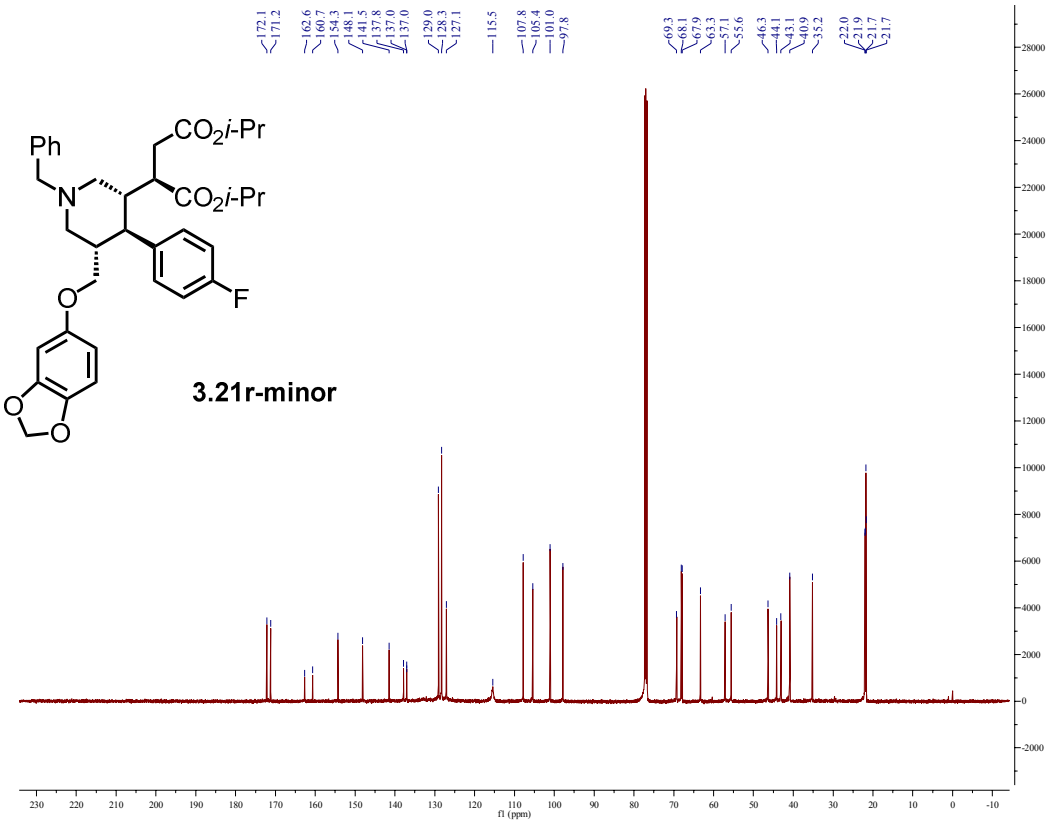

^{1}H NMR (600 MHz, CDCl$_3$)
CO$_2$i-Pr
Ph
Ph
TBSO
N
CO$_2$i-Pr
Ph
3.21q-minor
f1 (ppm)

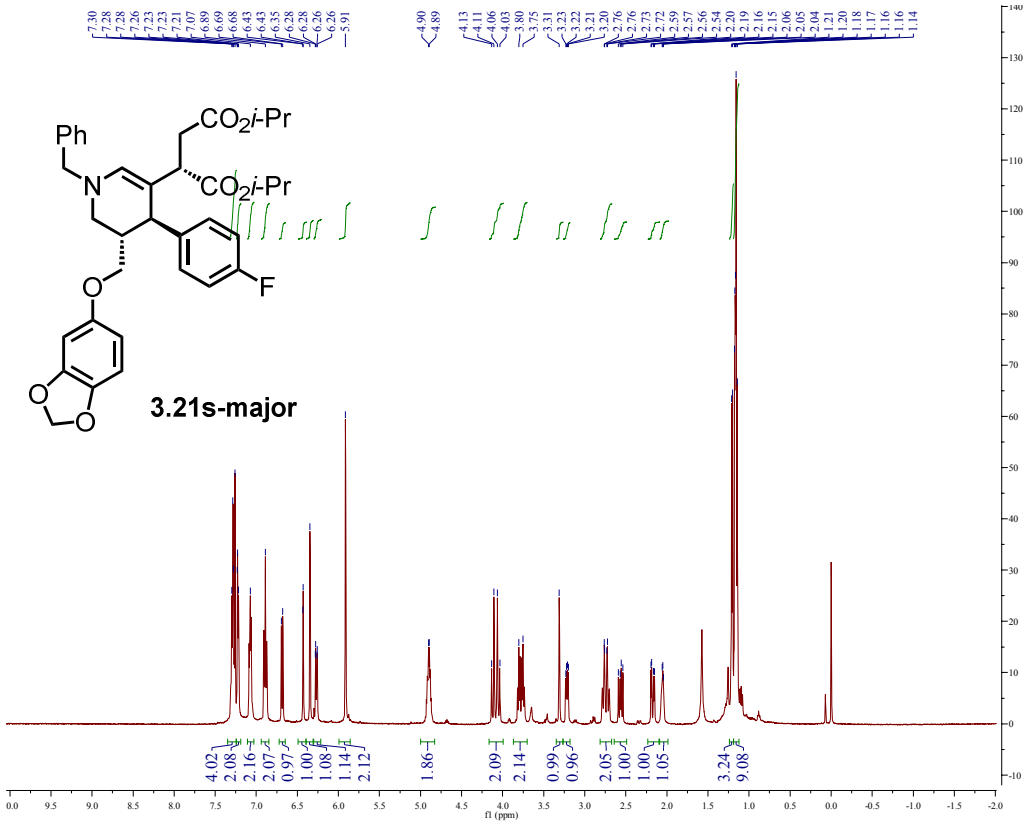

^{13}C NMR (151 MHz, CDCl$_3$)
CO$_2$i-Pr
Ph
Ph
TBSO
N
CO$_2$i-Pr
Ph
3.21q-minor
f1 (ppm)

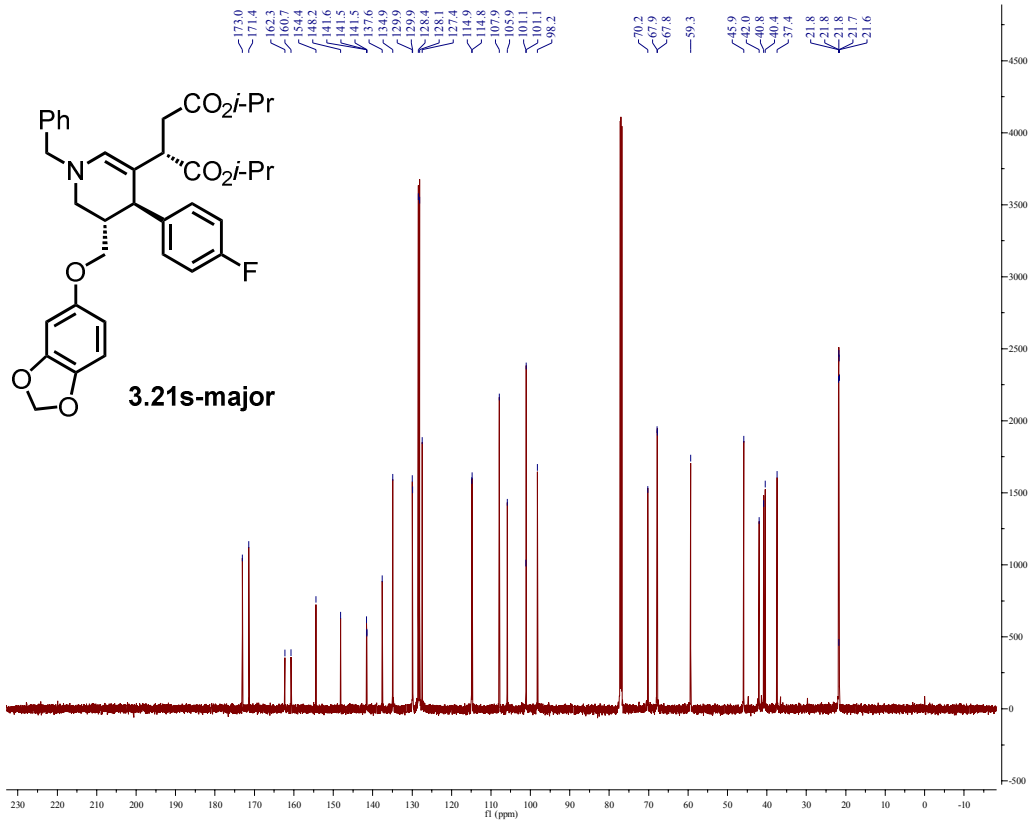

Ph
N
CO2i-Pr
CO2i-Pr
F
O
O
O
3.21r-major

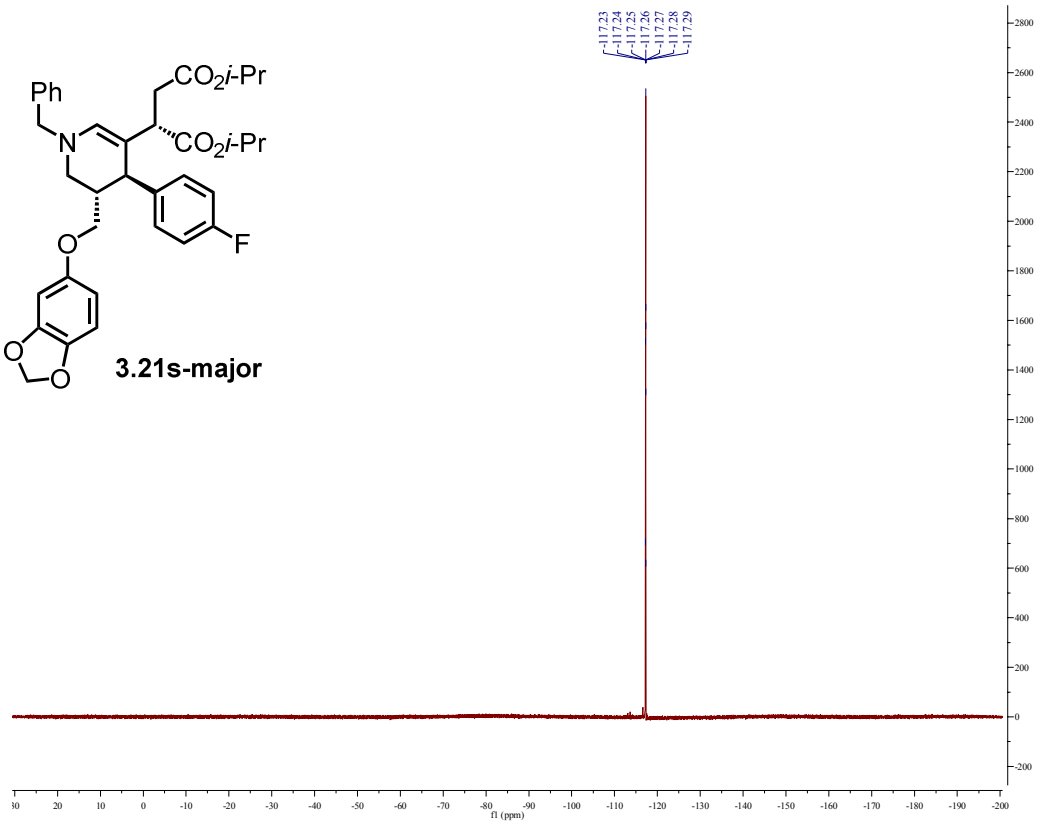

Ph
N
CO2i-Pr
CO2i-Pr
F
O
O
O
3.21r-major

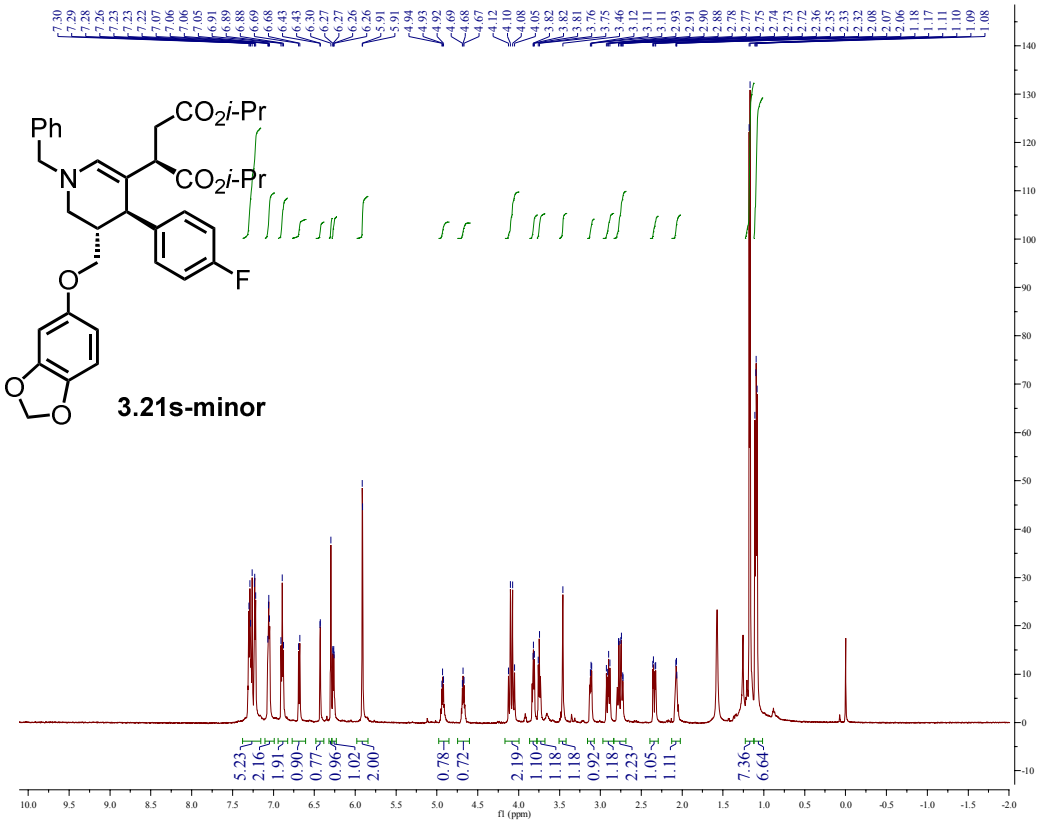

Ph
N
CO2i-Pr
CO2i-Pr
F
O
O
O
3.21r-minor

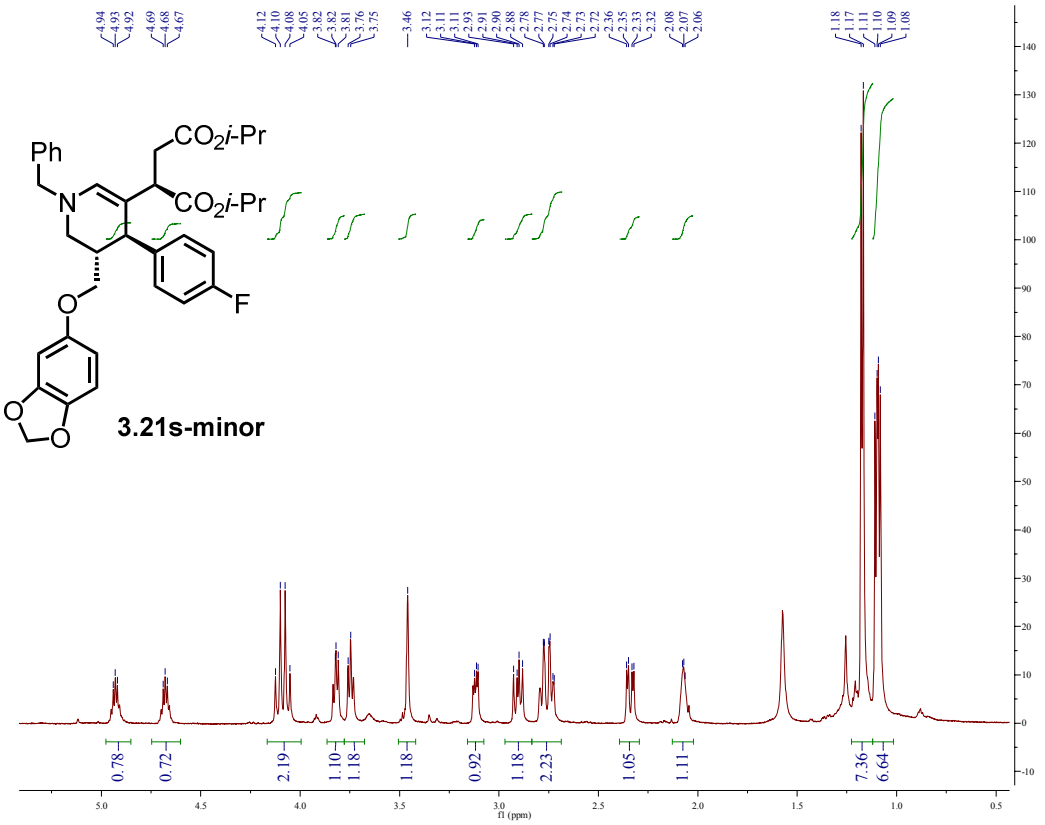

Ph
N
CO2i-Pr
CO2i-Pr
F
O
O
O
3.21r-minor

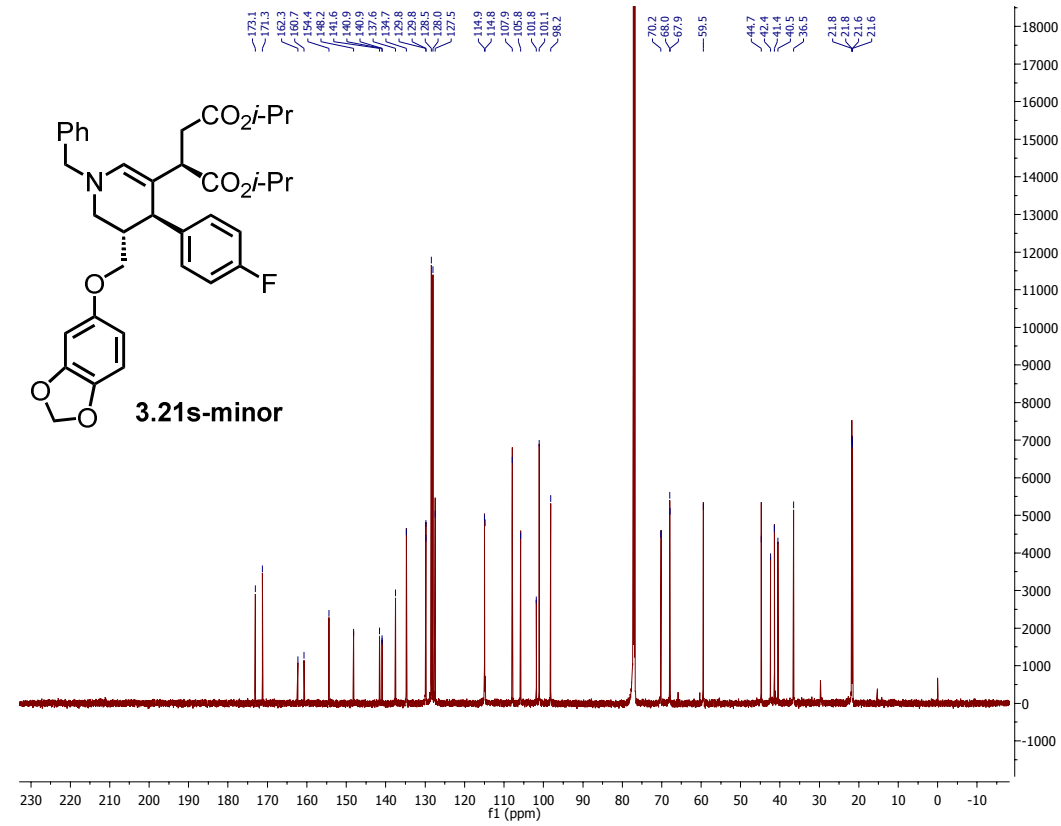

Ph
N
CO2i-Pr
CO2i-Pr
F
O
O
O
3.21s-major

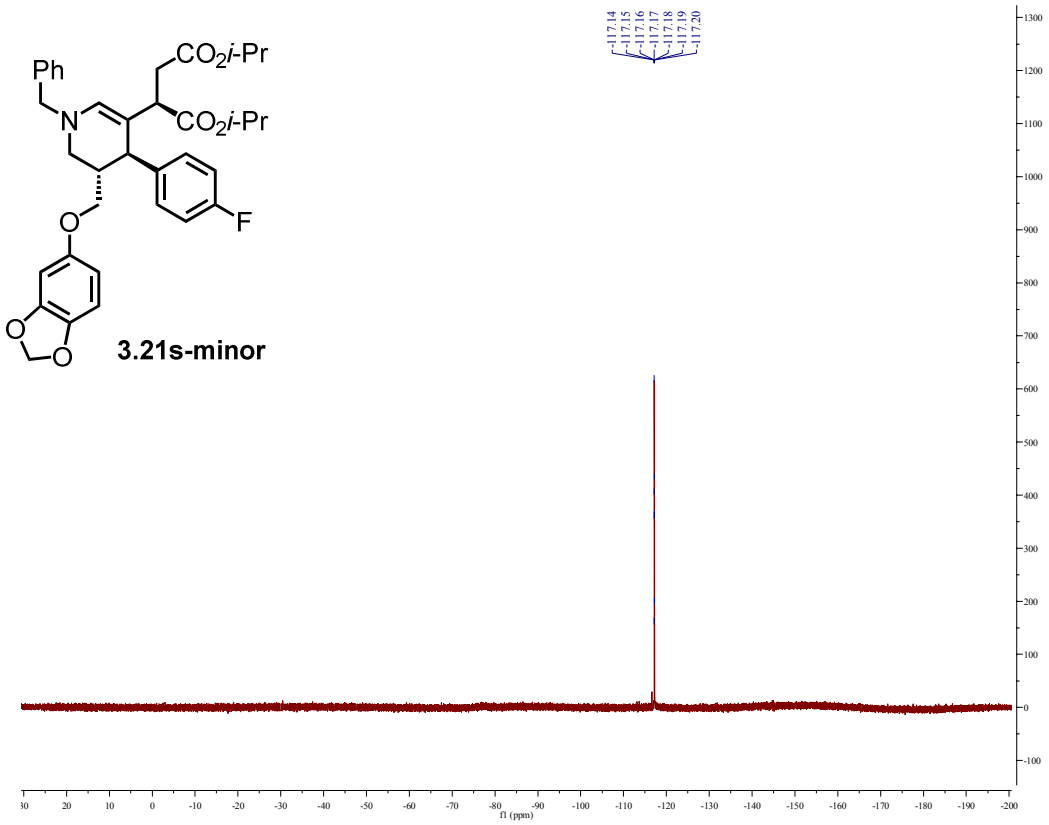

Ph
N
CO2i-Pr
CO2i-Pr
F
O
O
O
3.21s-major

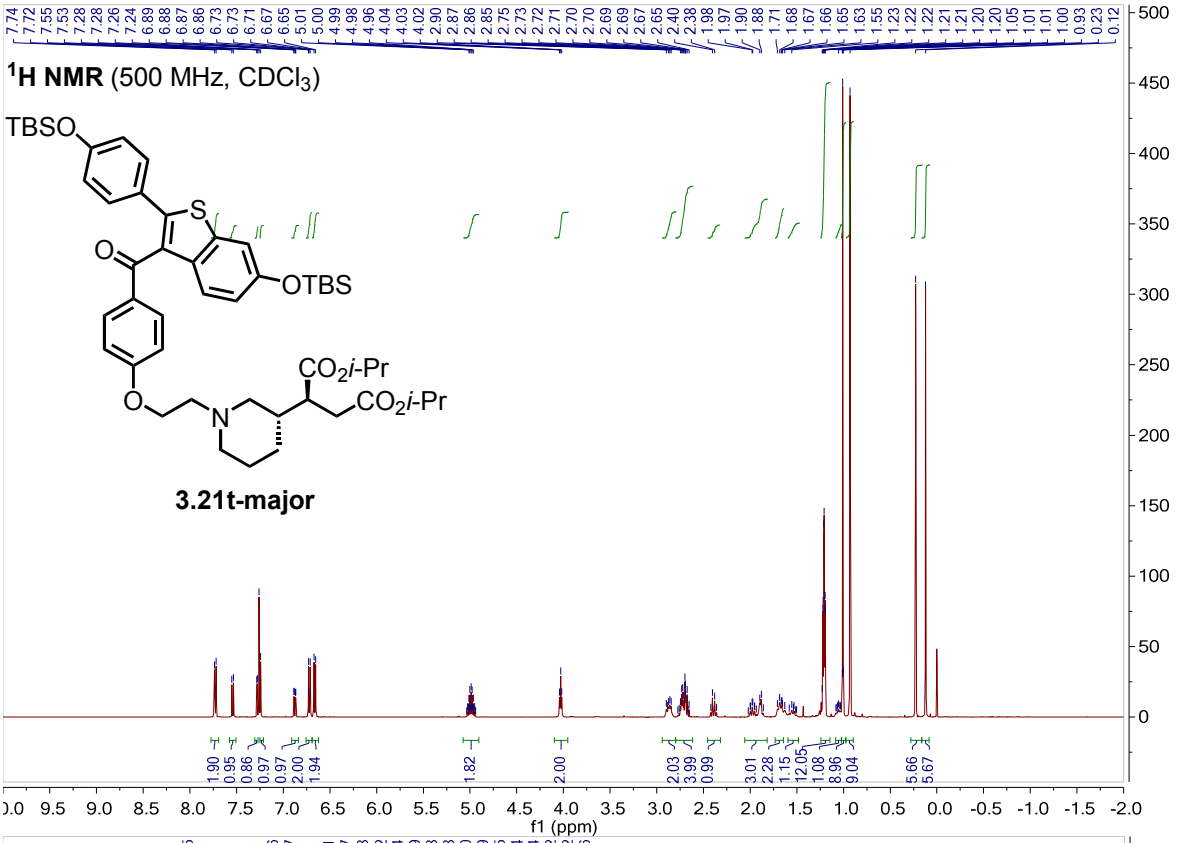

Ph
N
CO2i-Pr
CO2i-Pr
F
O
O
O
3.21s-major

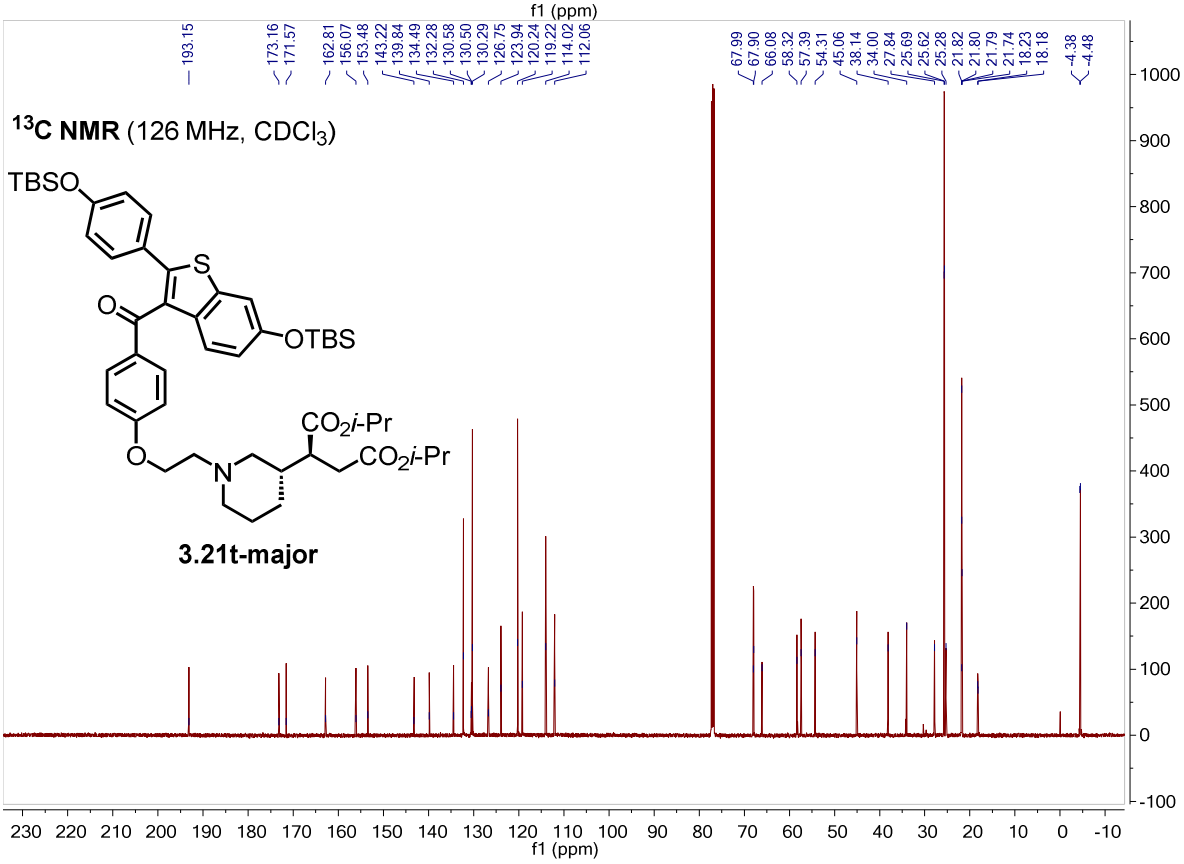

Ph
N
CO2i-Pr
CO2i-Pr
F
O
O
O
3.21s-minor

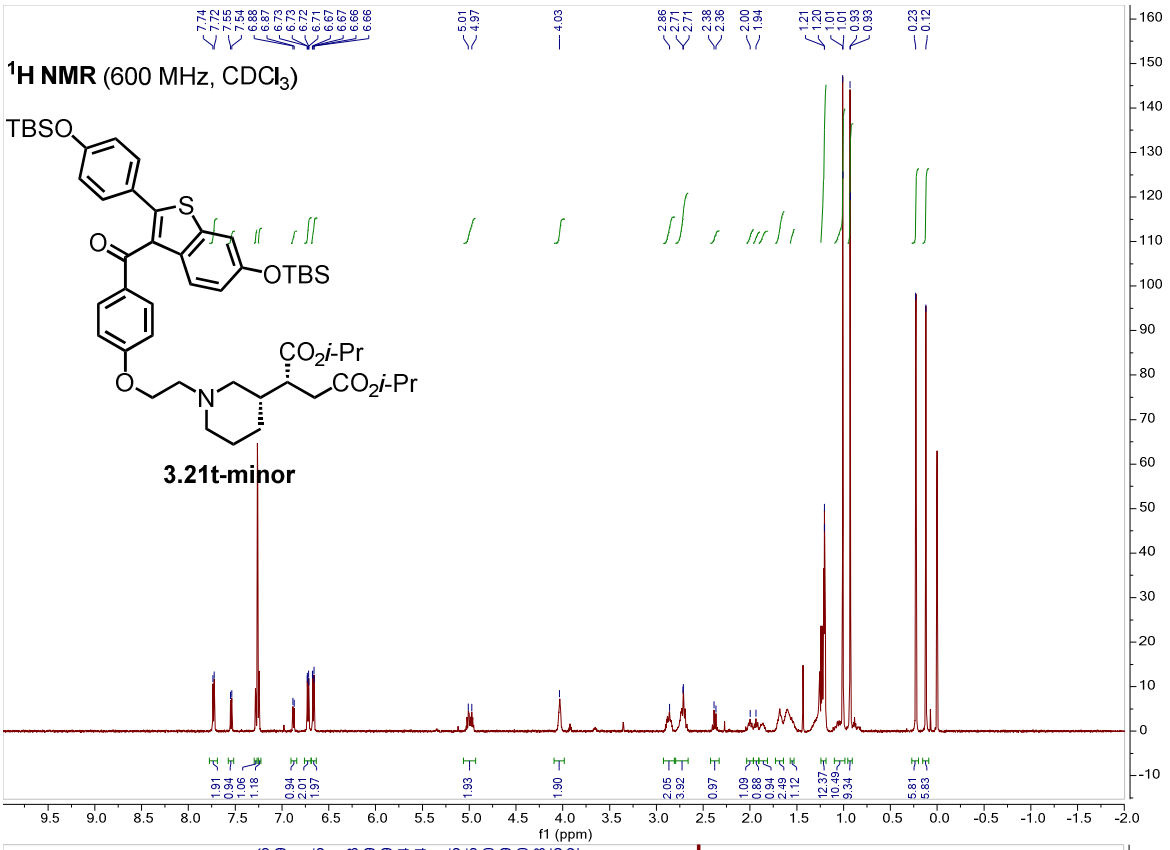

Ph
N
CO2i-Pr
CO2i-Pr
F
O
O
O
3.21s-minor
0.78
0.72
2.19
1.10
1.18
1.18
0.92
1.18
2.23
1.05
1.11
7.36
6.64
f1 (ppm)

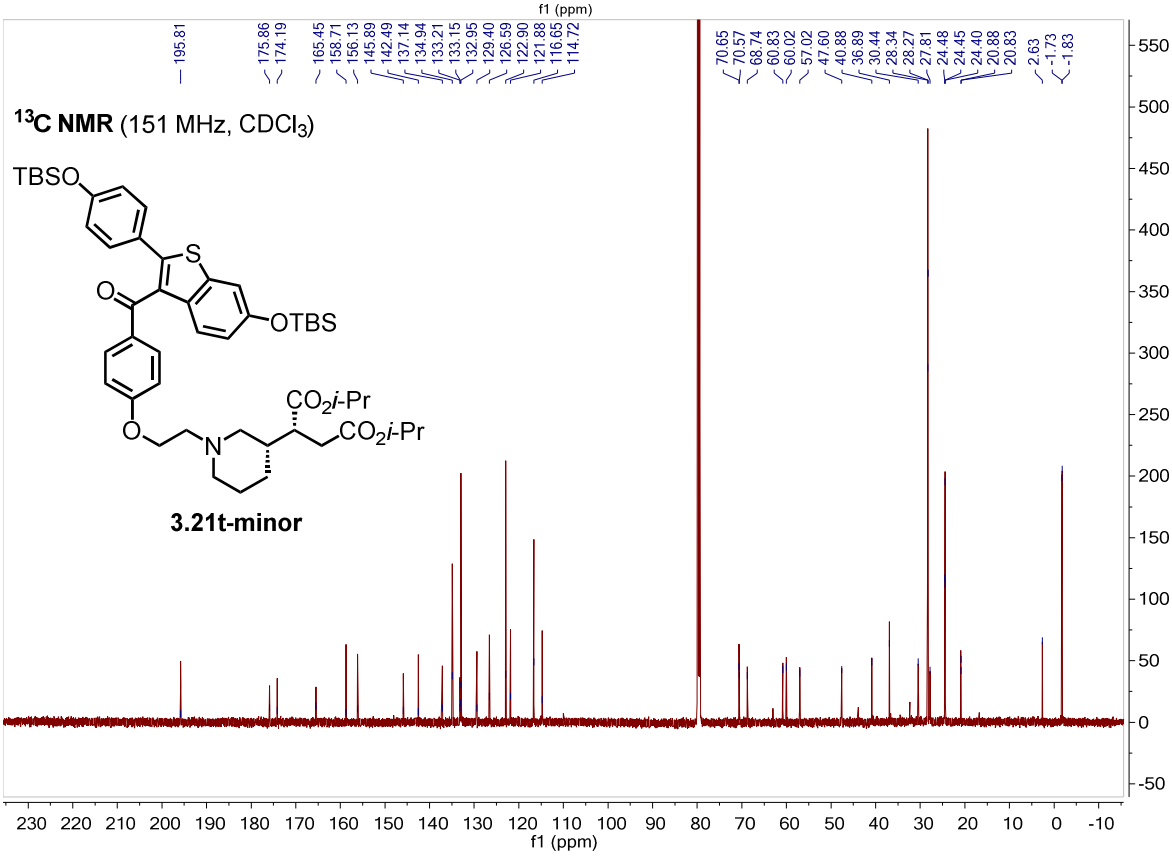

Ph
N
CO2i-Pr
CO2i-Pr
F
O
O
O
3.21s-minor
f1 (ppm)

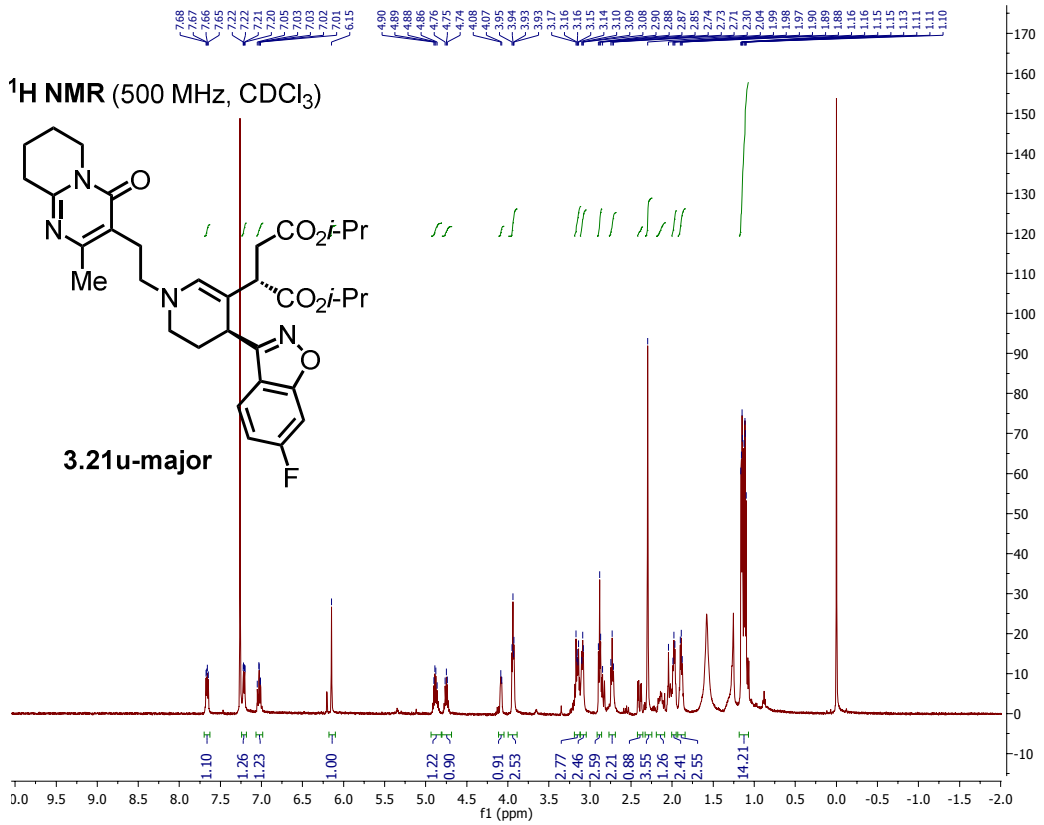

Ph
N
CO2i-Pr
CO2i-Pr
F
O
O
O
3.21s-minor
-117.14
-117.15
-117.16
-117.17
-117.18
-117.19
-117.20
f1 (ppm)

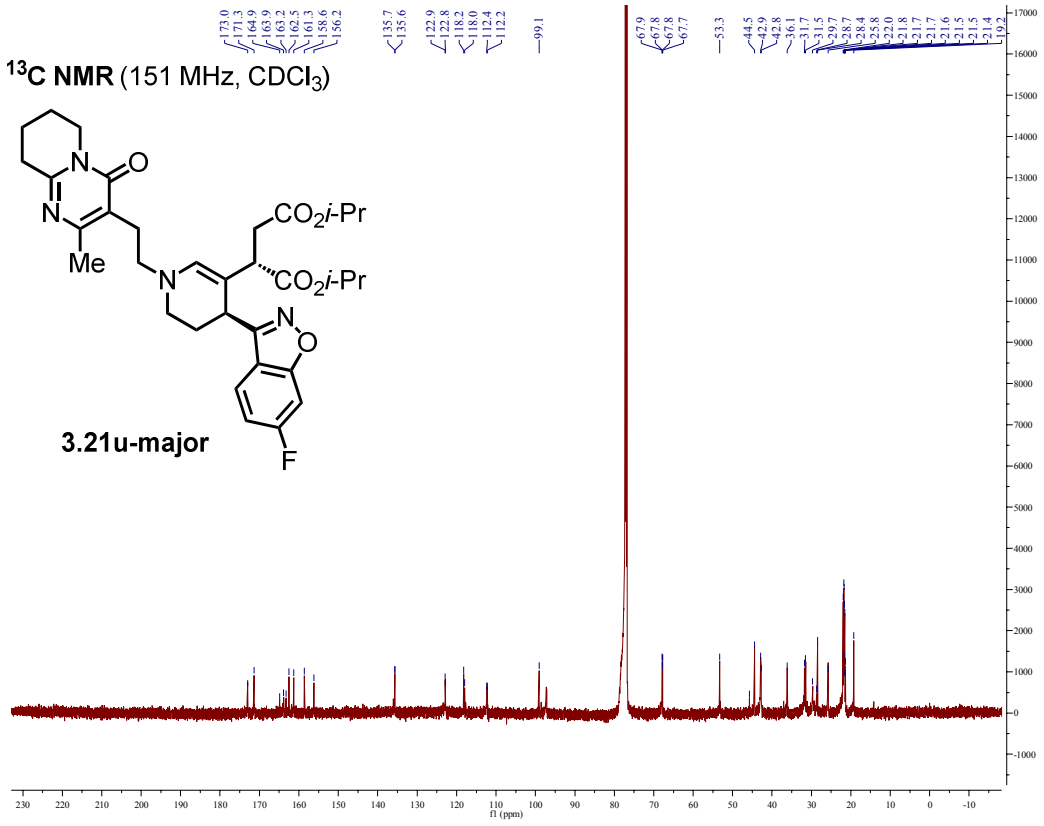

7.74 7.72 7.55 7.53 7.28 7.28 7.26 7.24 6.89 6.88 6.87 6.86 6.73 6.73 6.71 6.67 6.65 5.01 5.00 4.99 4.98 4.96 4.04 4.03 4.02 2.90 2.87 2.86 2.85 2.75 2.73 2.72 2.71 2.70 2.70 2.69 2.69 2.67 2.65 2.40 2.38 1.98 1.97 1.90 1.88 1.71 1.68 1.67 1.66 1.65 1.63 1.55 1.23 1.22 1.22 1.21 1.21 1.20 1.20 1.05 1.01 1.01 1.00 0.93 0.23 0.12
1H NMR (500 MHz, CDCl3)
TBSO
S
O
OTBS
CO2i-Pr
CO2i-Pr
O
N
3.21t-major
1.90 0.95 0.86 0.97 0.97 2.00 1.94 1.82 2.00 2.03 3.99 0.99 3.01 2.28 1.15 12.05 1.08 8.96 9.04 5.66 5.67
f1 (ppm)


193.15 173.16 171.57 162.81 156.07 153.48 143.22 139.84 134.49 132.28 130.58 130.50 130.29 126.75 123.94 120.24 119.22 114.02 112.06 67.99 67.90 66.08 58.32 57.39 54.31 45.06 38.14 34.00 27.84 25.69 25.62 25.28 21.82 21.80 21.79 21.74 18.23 18.18 -4.38 -4.48
13C NMR (126 MHz, CDCl3)
TBSO
S
O
OTBS
CO2i-Pr
CO2i-Pr
O
N
3.21t-major
f1 (ppm)

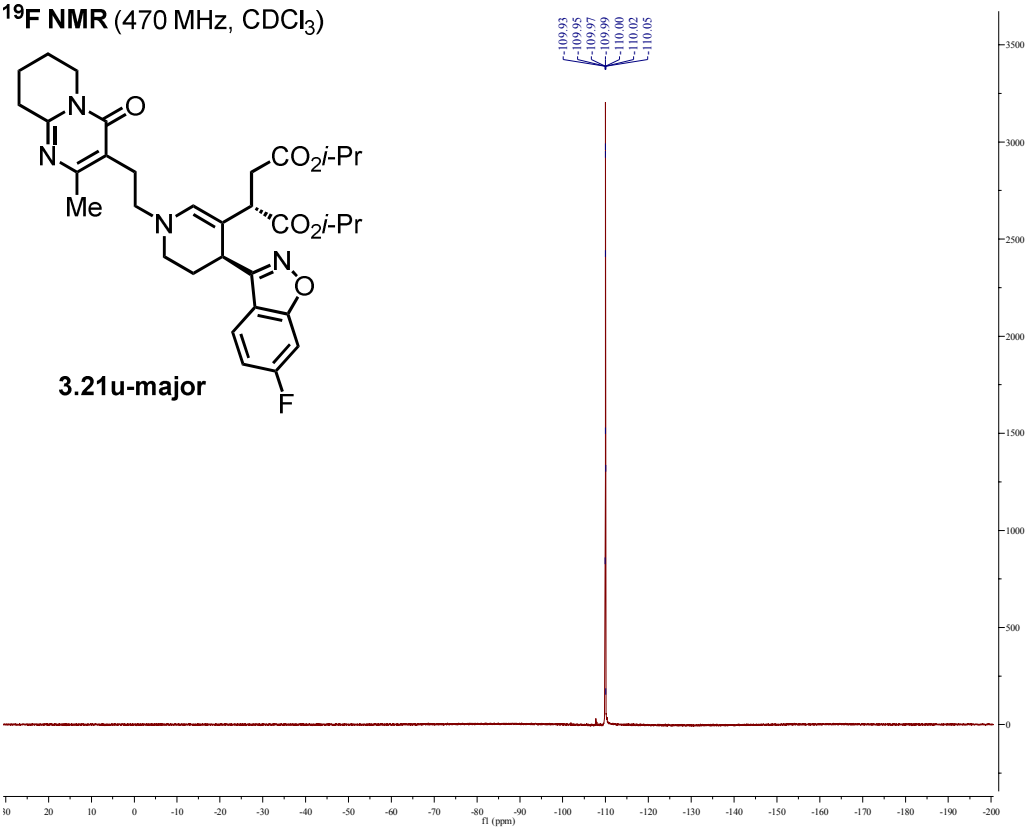

7.74
7.72
7.55
7.54
6.88
6.87
6.73
6.73
6.72
6.71
6.67
6.67
6.66
6.66
5.01
4.97
4.03
2.86
2.71
2.71
2.38
2.36
2.00
1.94
1.21
1.20
1.01
1.01
0.93
0.93
0.23
0.12
1H NMR (600 MHz, CDCl3)
TBSO
S
O
OTBS
CO2i-Pr
O
N
CO2i-Pr
3.21t-minor
1.91
0.94
1.06
1.18
0.94
2.01
1.97
1.93
1.90
2.05
3.92
0.97
1.09
0.88
0.94
2.49
1.12
12.37
10.49
9.34
5.81
5.83
f1 (ppm)


195.81
175.86
174.19
165.45
158.71
156.13
145.89
142.49
137.14
134.94
133.21
133.15
132.95
129.40
126.59
122.90
121.88
116.65
114.72
70.65
70.57
68.74
60.83
60.02
57.02
47.60
40.88
36.89
30.44
28.34
28.27
27.81
24.48
24.45
24.40
20.88
20.83
2.63
-1.73
-1.83
13C NMR (151 MHz, CDCl3)
TBSO
S
O
OTBS
CO2i-Pr
O
N
CO2i-Pr
3.21t-minor
f1 (ppm)

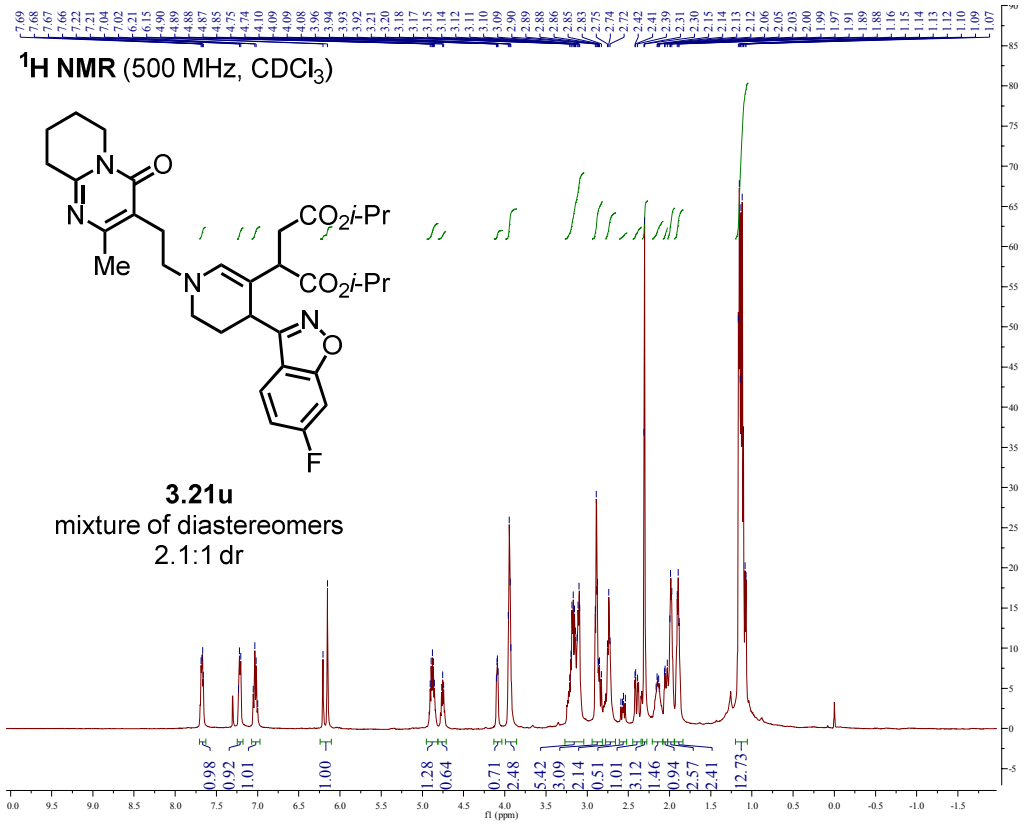

1H NMR (500 MHz, CDCl3)
CO2i-Pr
CO2i-Pr
Me
N
O
F
3.21u-major
f1 (ppm)

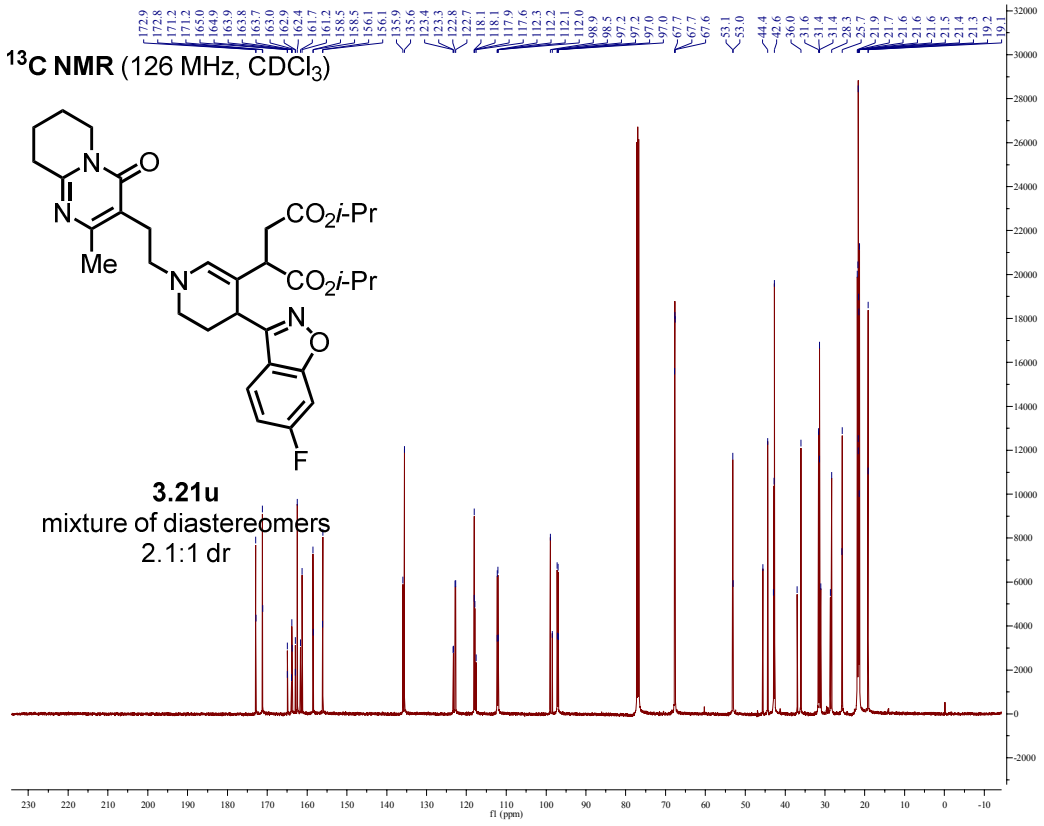

13C NMR (151 MHz, CDCl3)
CO2i-Pr
CO2i-Pr
Me
N
O
F
3.21u-major
f1 (ppm)

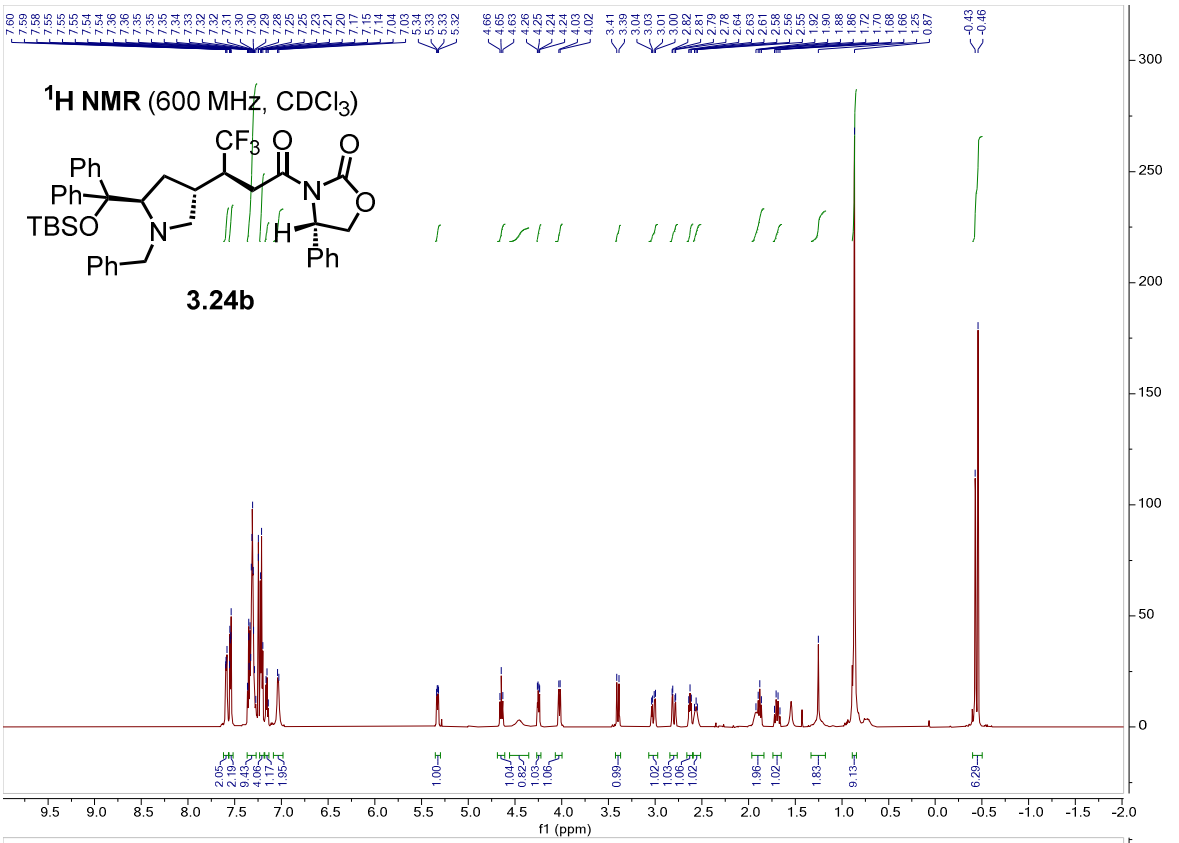
^{19}F NMR (470 MHz, $CDCl_3$)

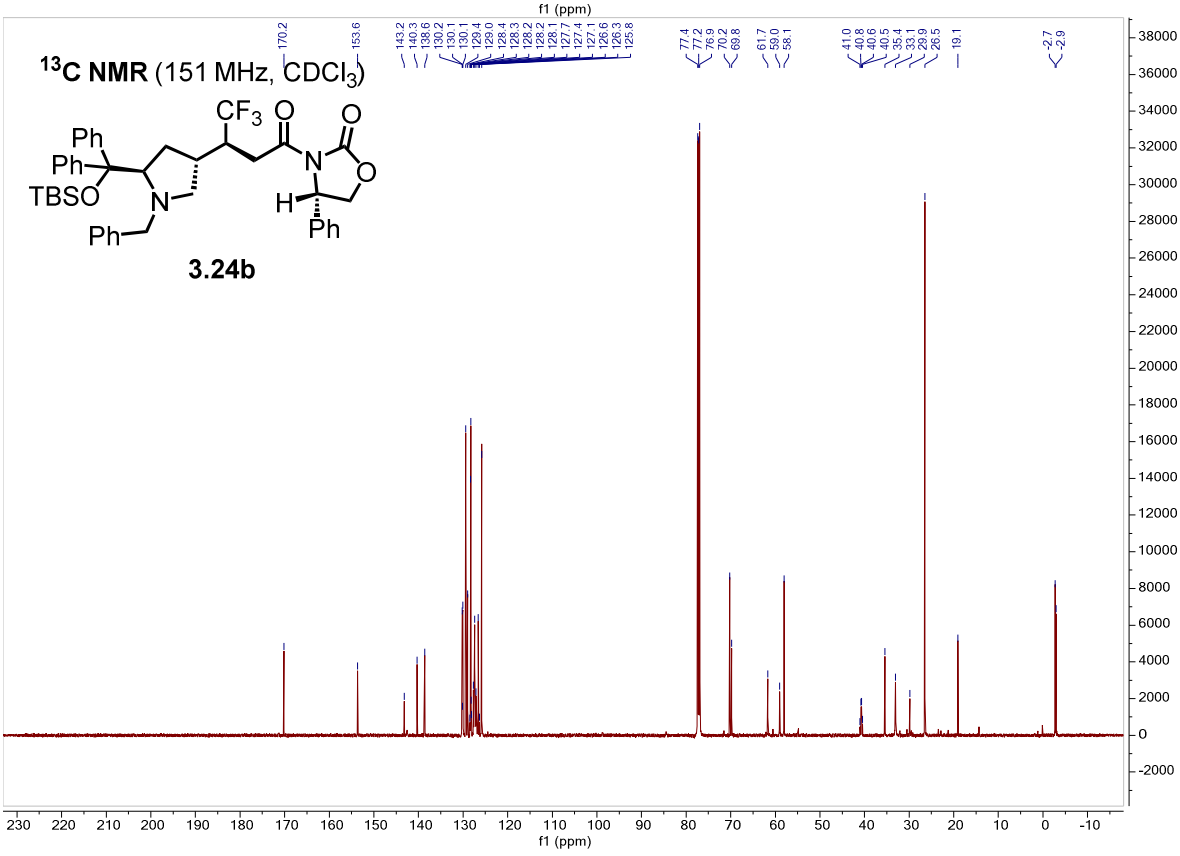


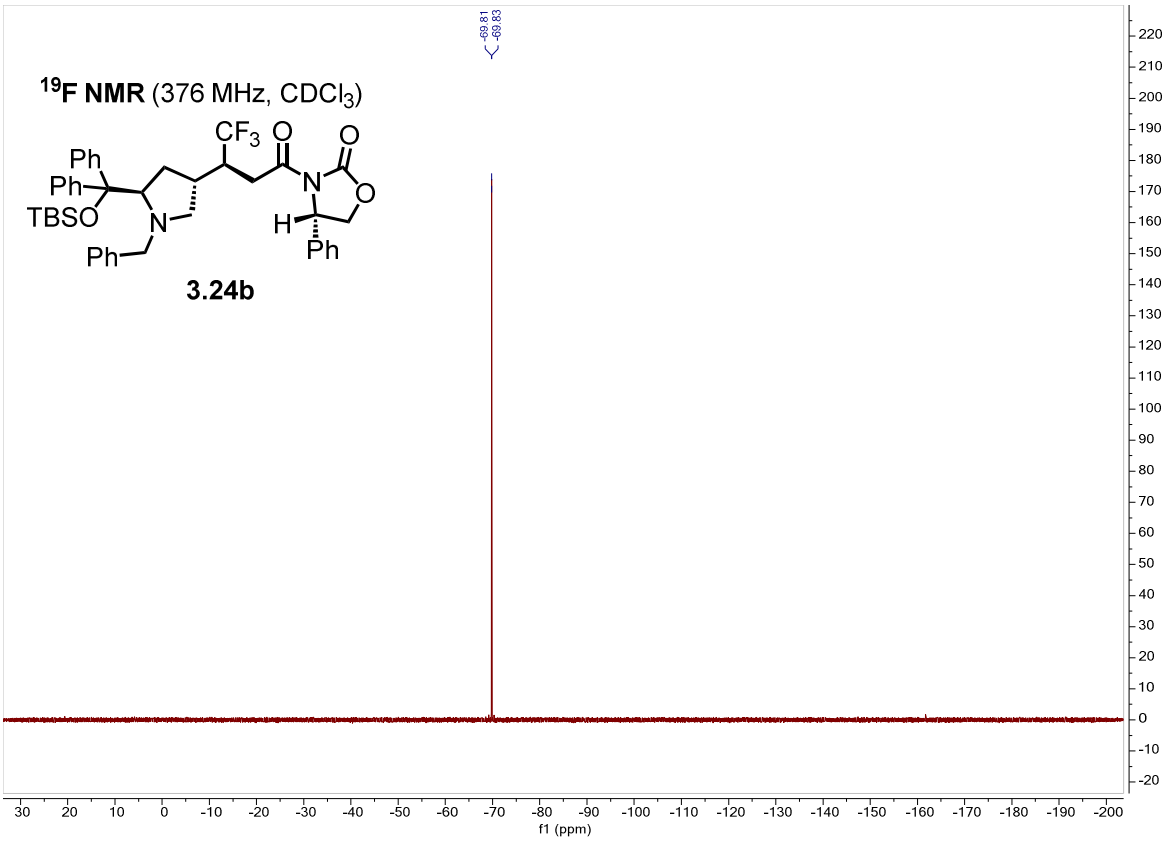
3.21u-major

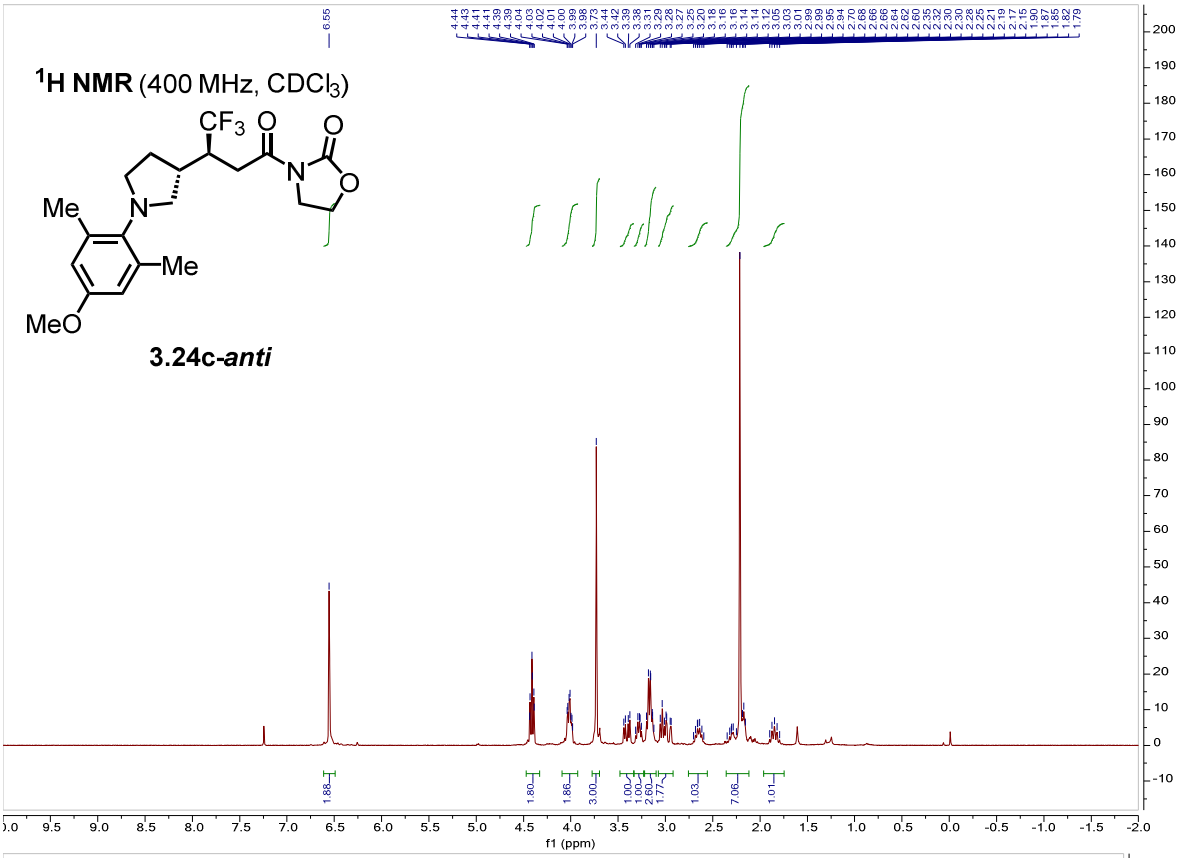

^{1}H NMR (500 MHz, CDCl$_3$)
CO$_2$i-Pr
CO$_2$i-Pr
Me
F
3.21u
mixture of diastereomers
2.1:1 dr

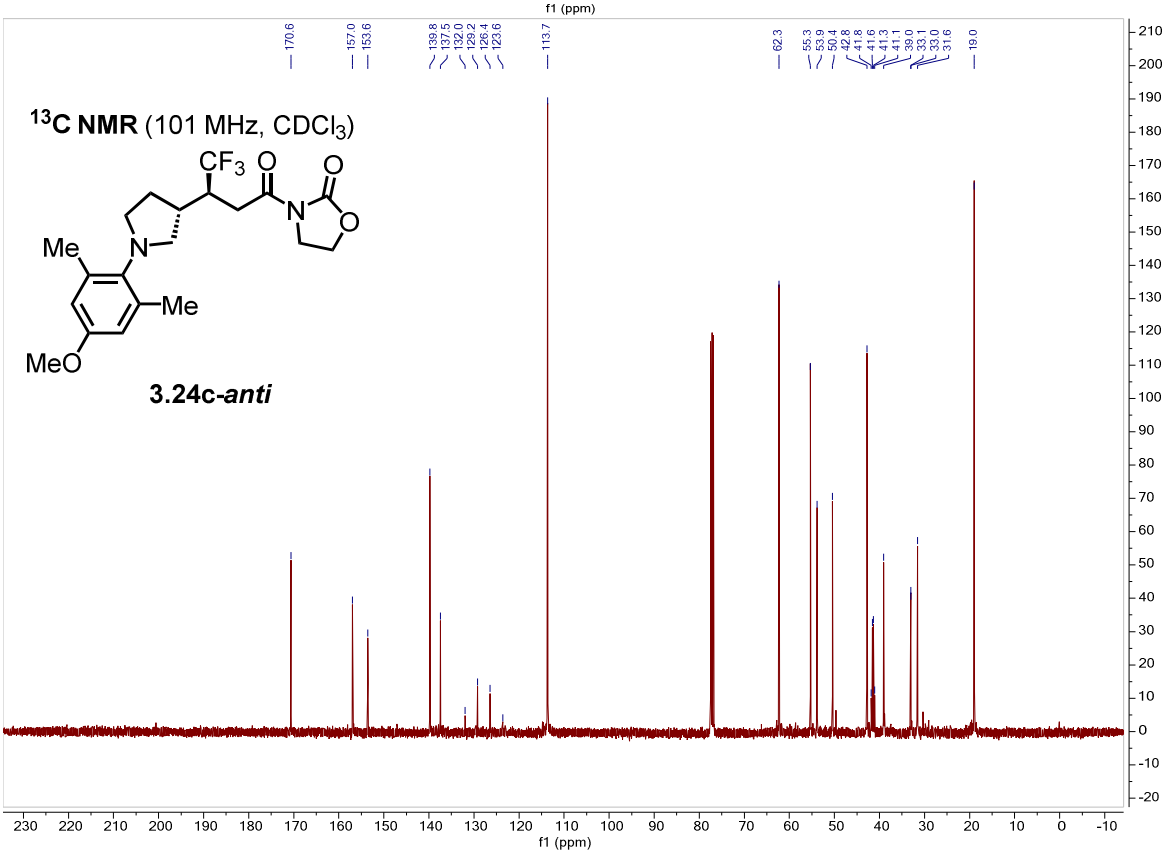

^{13}C NMR (126 MHz, CDCl$_3$)
CO$_2$i-Pr
CO$_2$i-Pr
Me
F
3.21u
mixture of diastereomers
2.1:1 dr

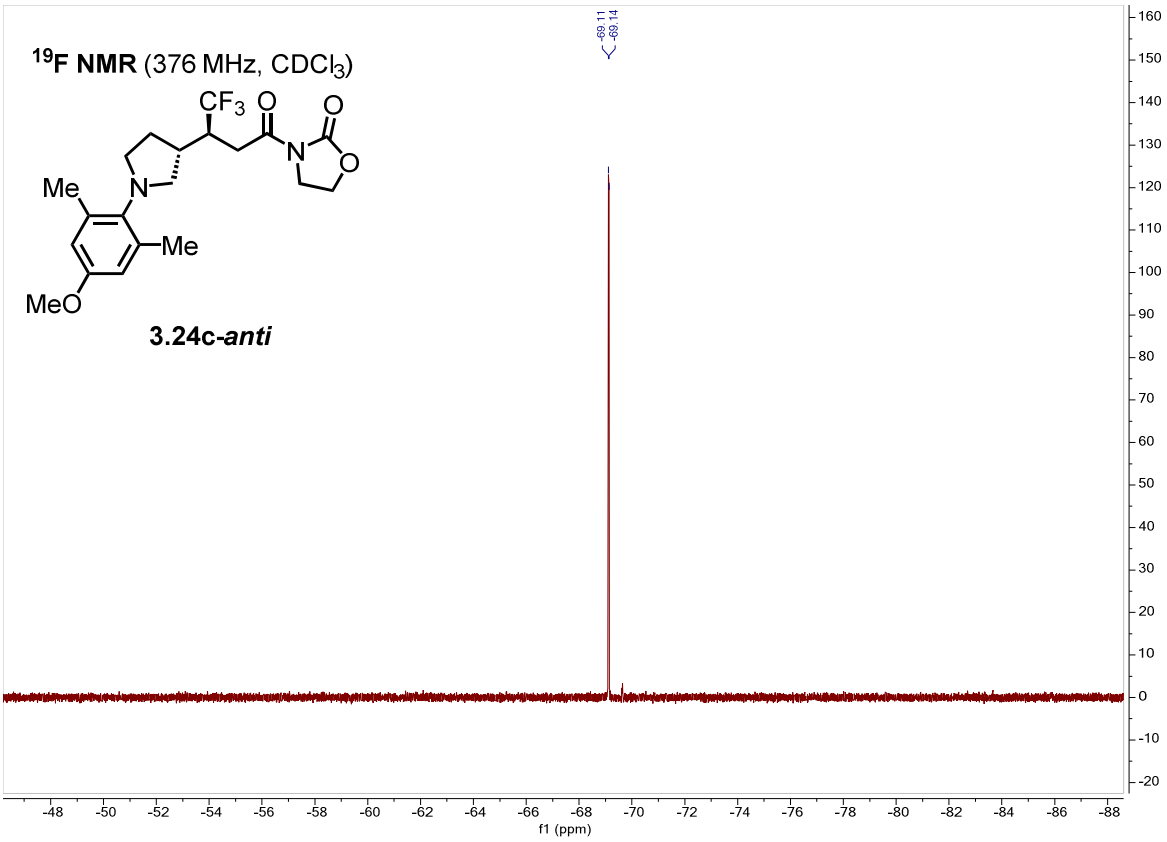

^{1}H NMR (600 MHz, $CDCl_3$)
3.24b
f1 (ppm)

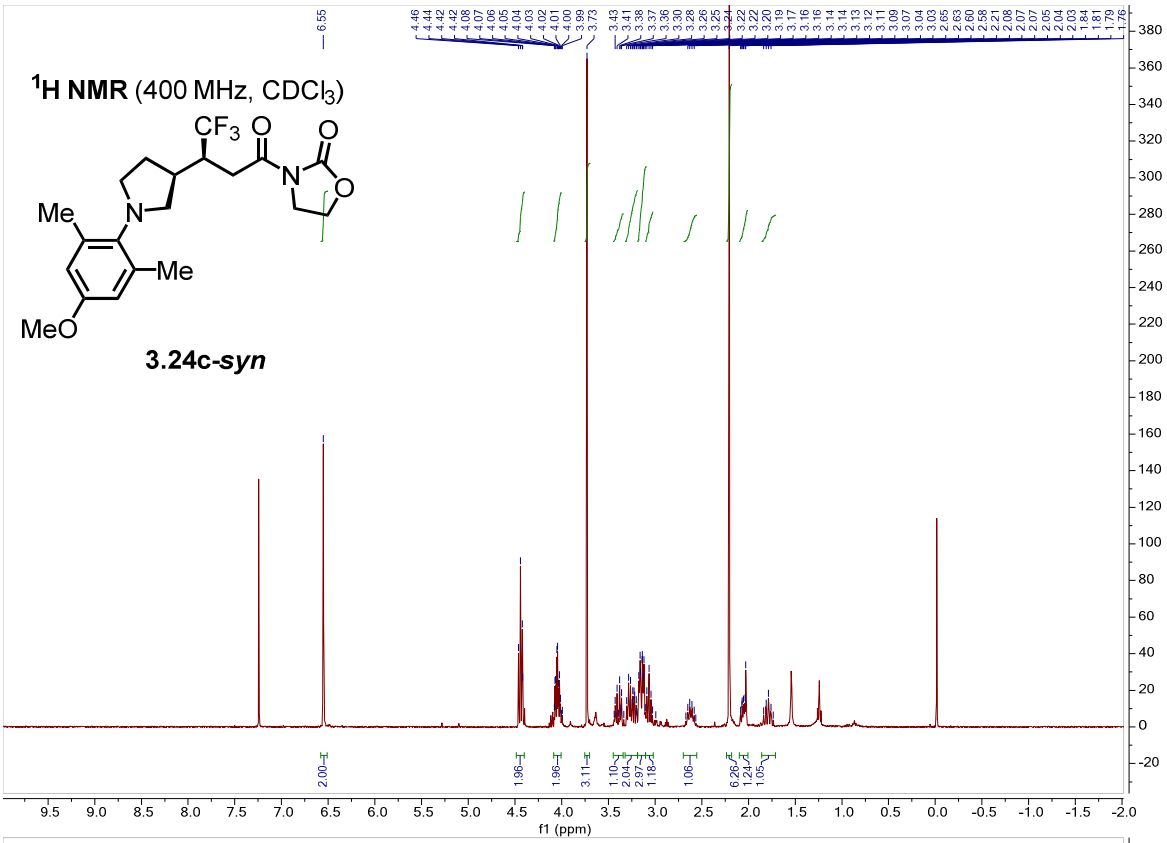

^{13}C NMR (151 MHz, $CDCl_3$)
3.24b
f1 (ppm)

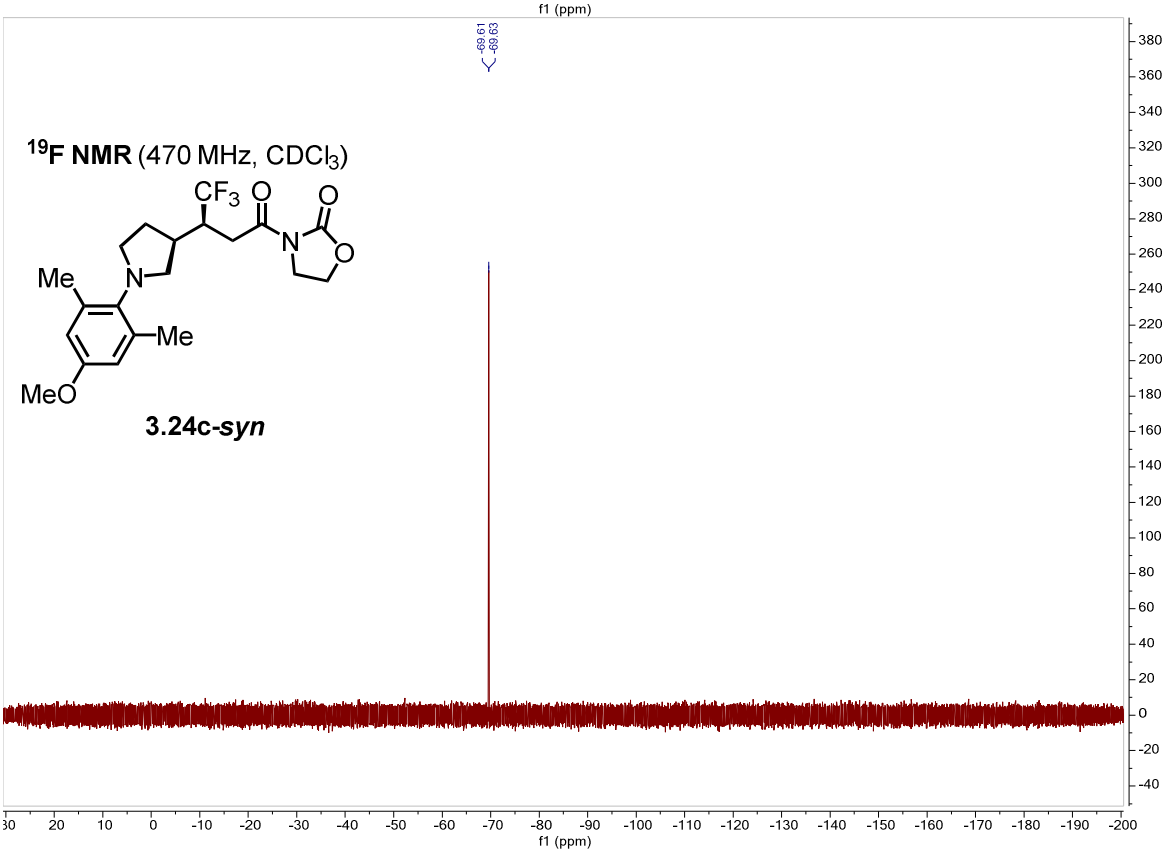

-69.81
-69.83
19F NMR (376 MHz, CDCl3)
CF3
O
O
Ph
Ph
TBSO
N
N
O
H
Ph
Ph
3.24b
f1 (ppm)

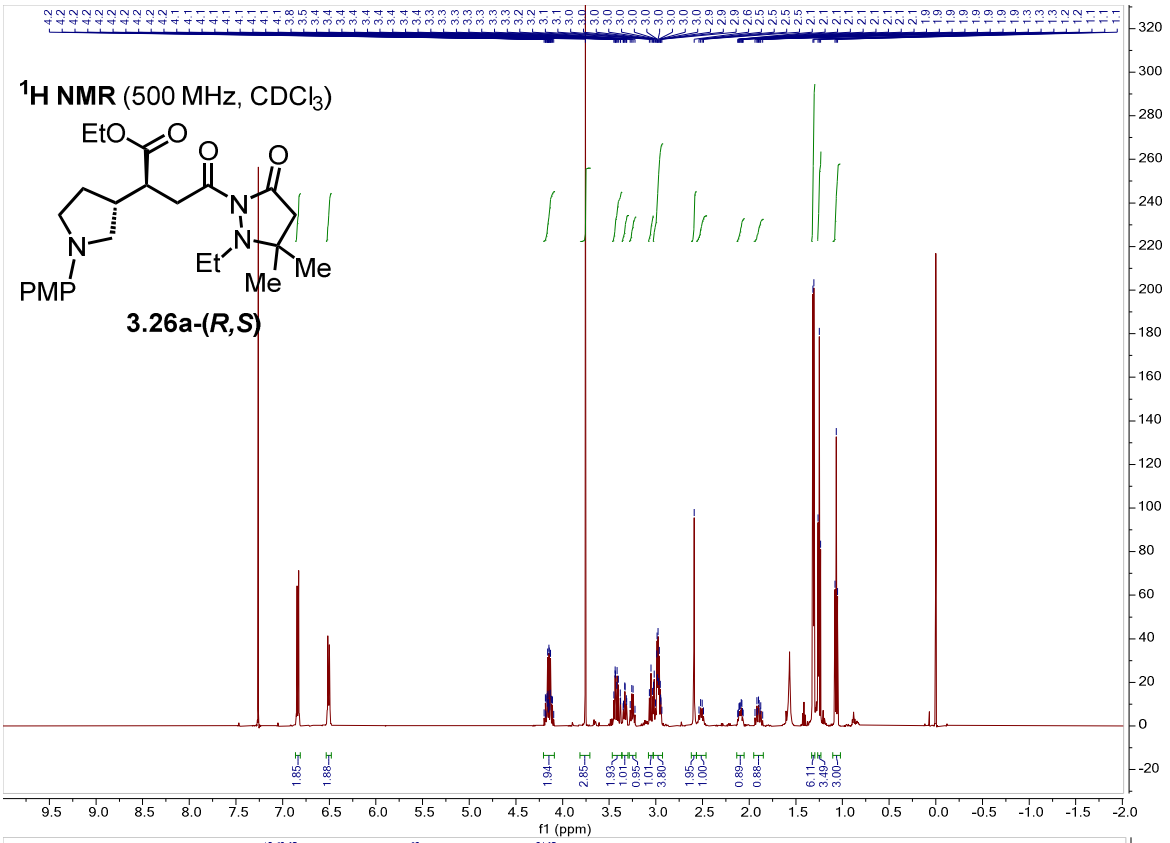

^{1}H NMR (400 MHz, $CDCl_3$)
CF_3 O
O
N
O
Me
N
Me
MeO
3.24c-*anti*
f1 (ppm)

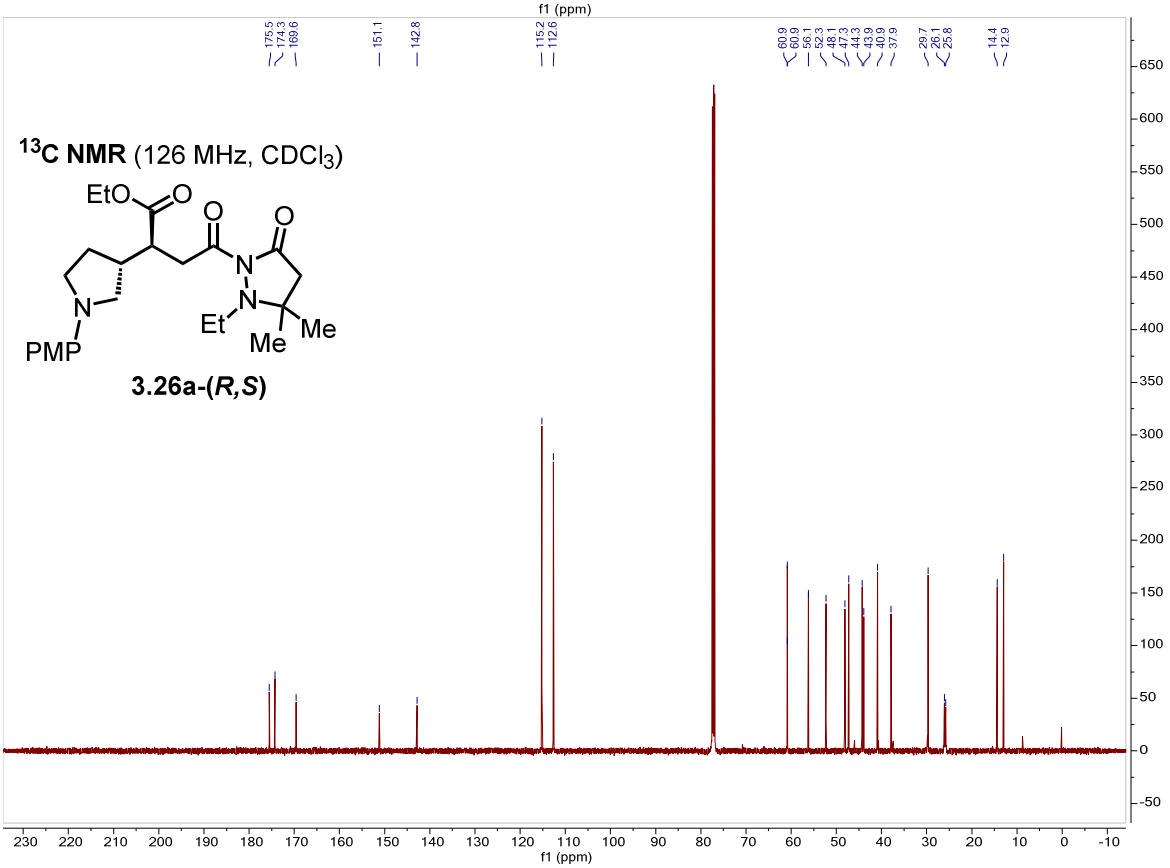

^{13}C NMR (101 MHz, $CDCl_3$)
CF_3 O
O
N
O
Me
N
Me
MeO
3.24c-*anti*
f1 (ppm)

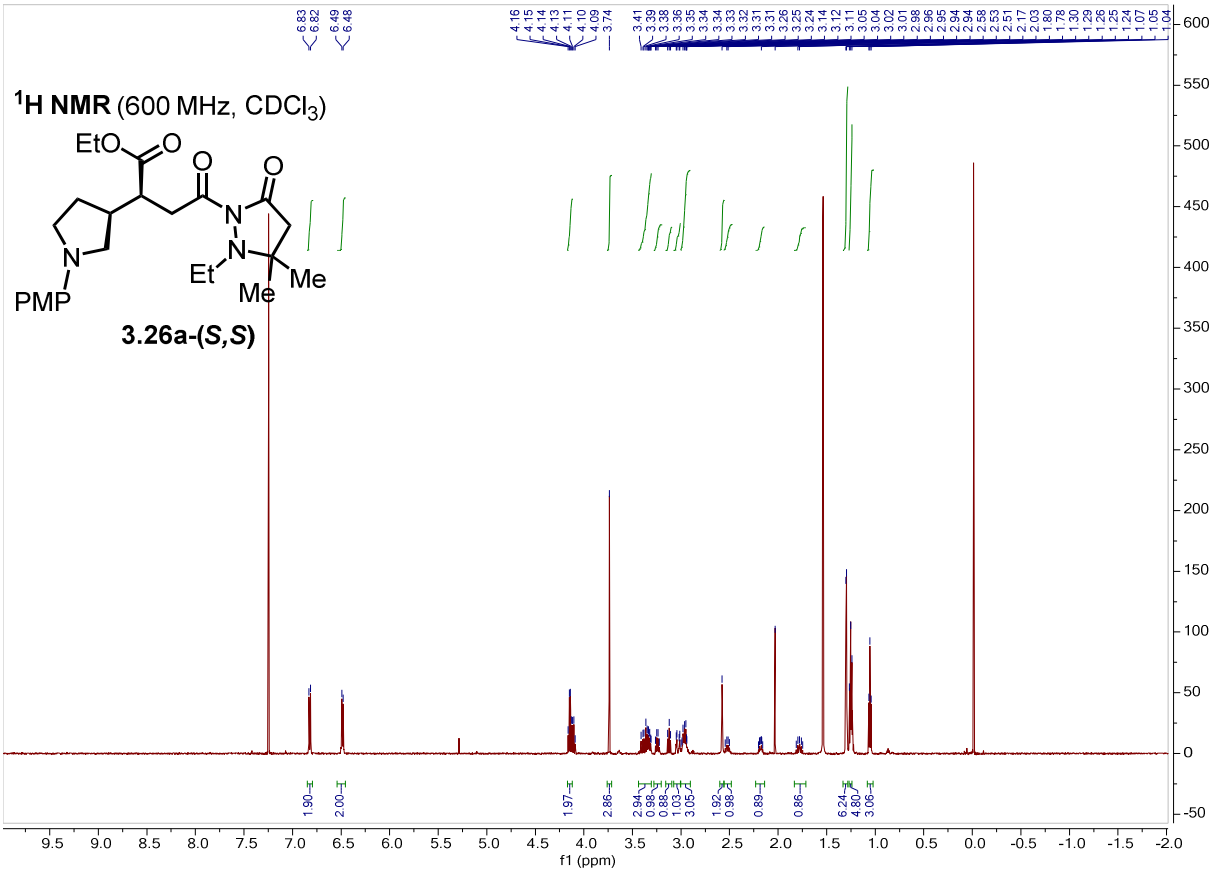

19F NMR (376 MHz, CDCl3)
CF3
O
O
N
O
Me
N
Me
MeO
3.24c-anti
-69.11
-69.14
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-48
-50
-52
-54
-56
-58
-60
-62
-64
-66
-68
-70
-72
-74
-76
-78
-80
-82
-84
-86
-88
f1 (ppm)

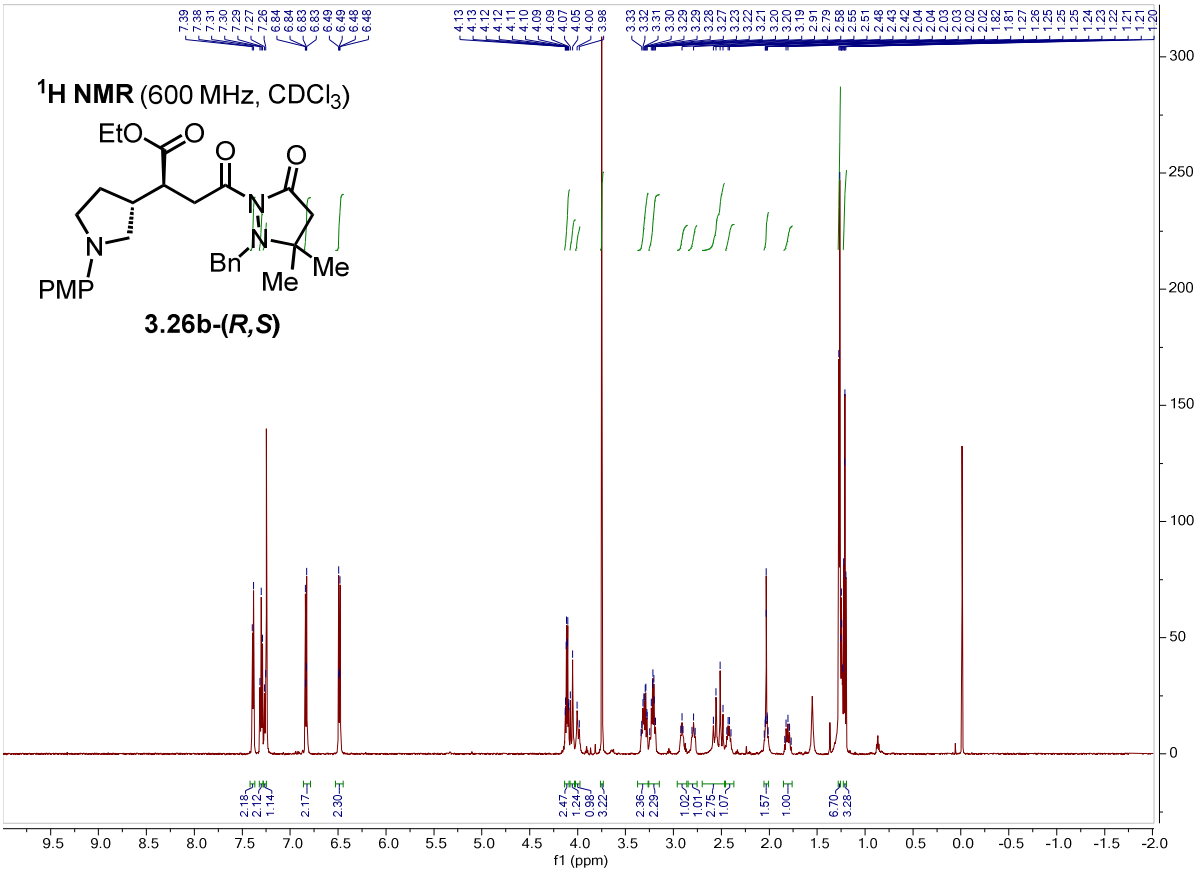

^{1}H NMR (400 MHz, $CDCl_3$)
CF_3 O O
N
Me
N
Me
MeO
3.24c-*syn*
f1 (ppm)


^{19}F NMR (470 MHz, $CDCl_3$)
CF_3 O O
N
Me
N
Me
MeO
3.24c-*syn*
f1 (ppm)

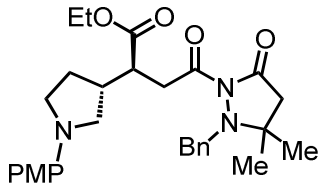

^{1}H NMR (500 MHz, CDCl$_3$)
EtO
O
O
O
N
N
N
Et
Me
Me
PMP
3.26a-(*R,S*)
f1 (ppm)


^{13}C NMR (126 MHz, CDCl$_3$)
EtO
O
O
O
N
N
N
Et
Me
Me
PMP
3.26a-(*R,S*)
f1 (ppm)

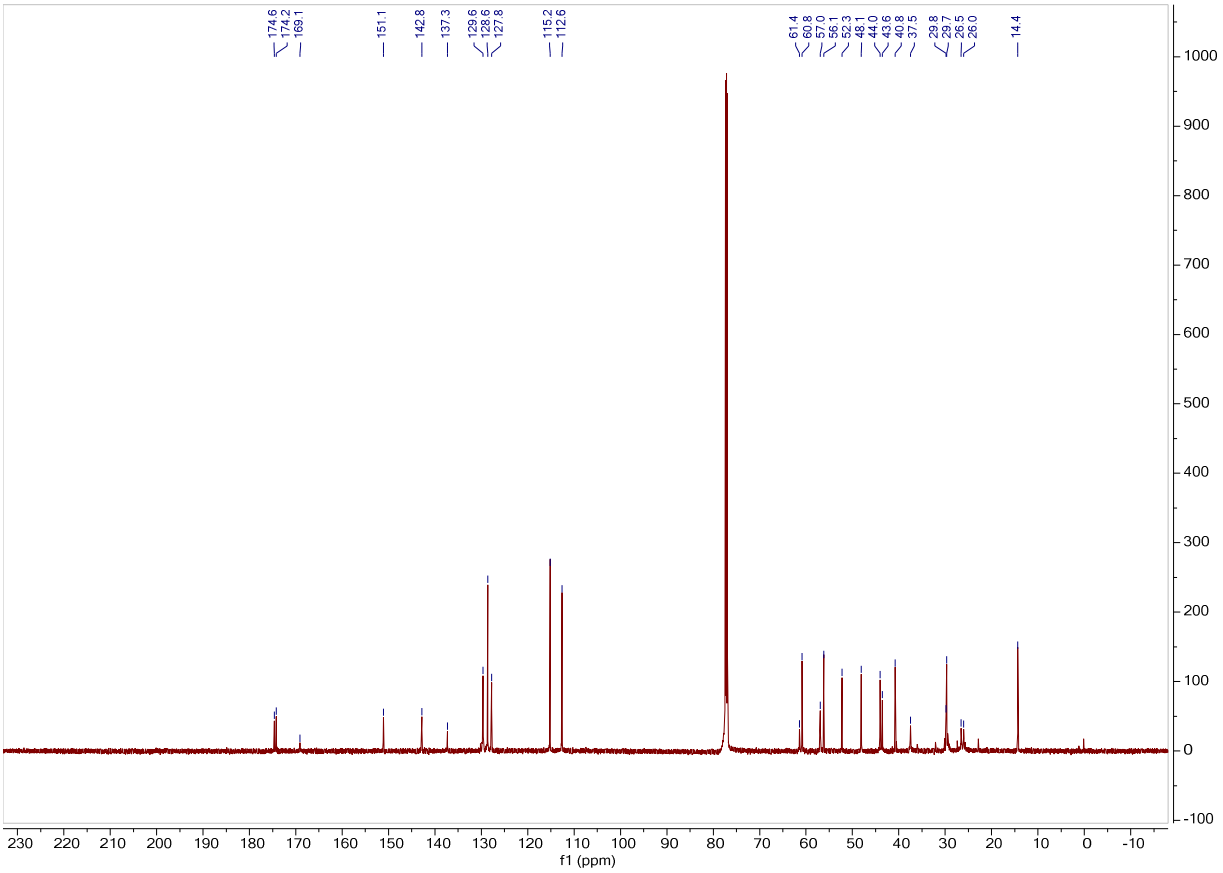

1H NMR (600 MHz, CDCl3)
EtO
O
O
O
N
N
N
Et
Me
Me
PMP
3.26a-(S,S)
f1 (ppm)

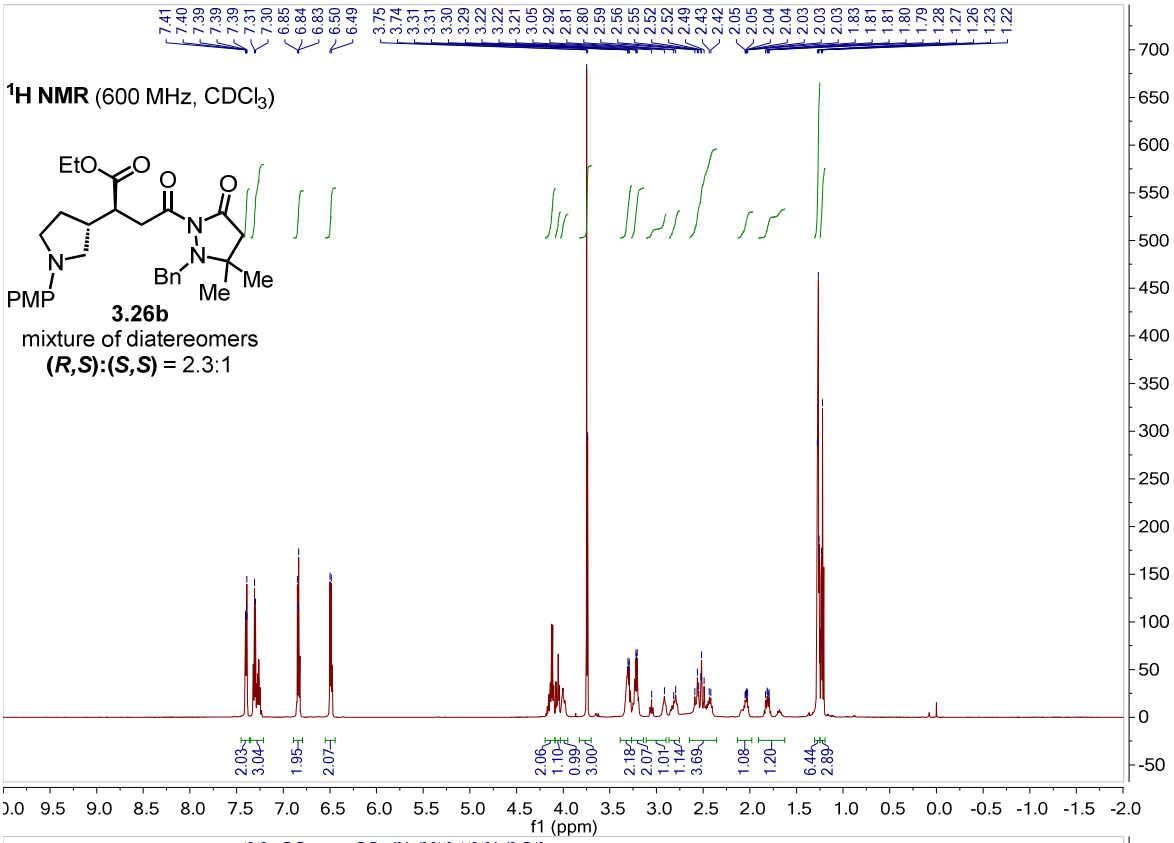


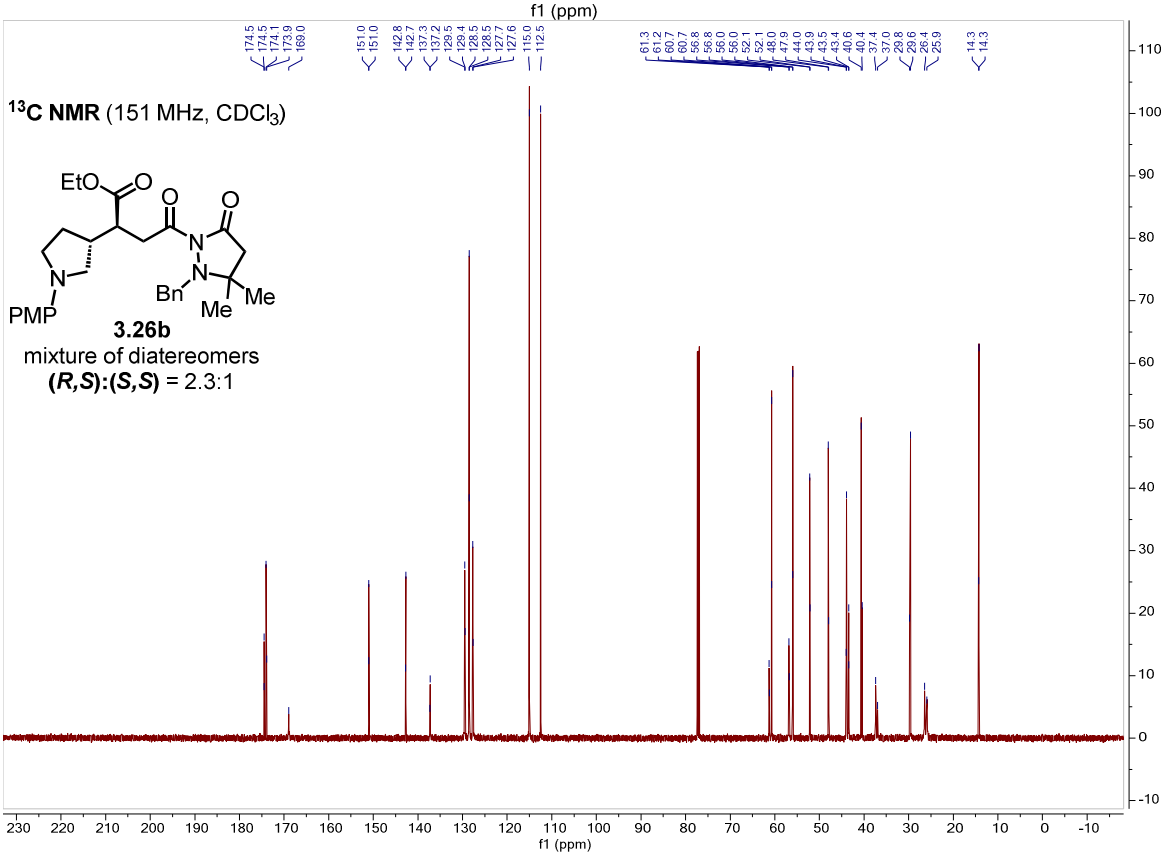
^{13}C NMR (151 MHz, $CDCl_3$)

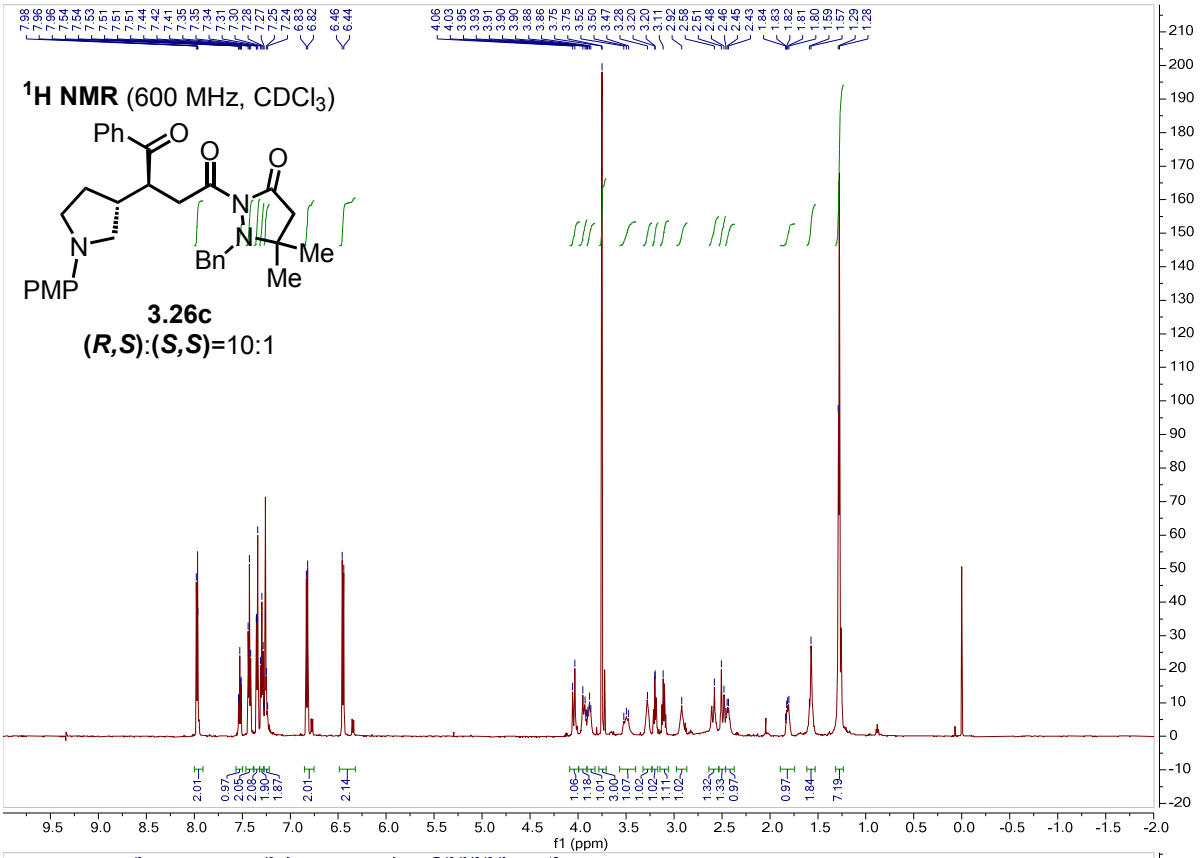


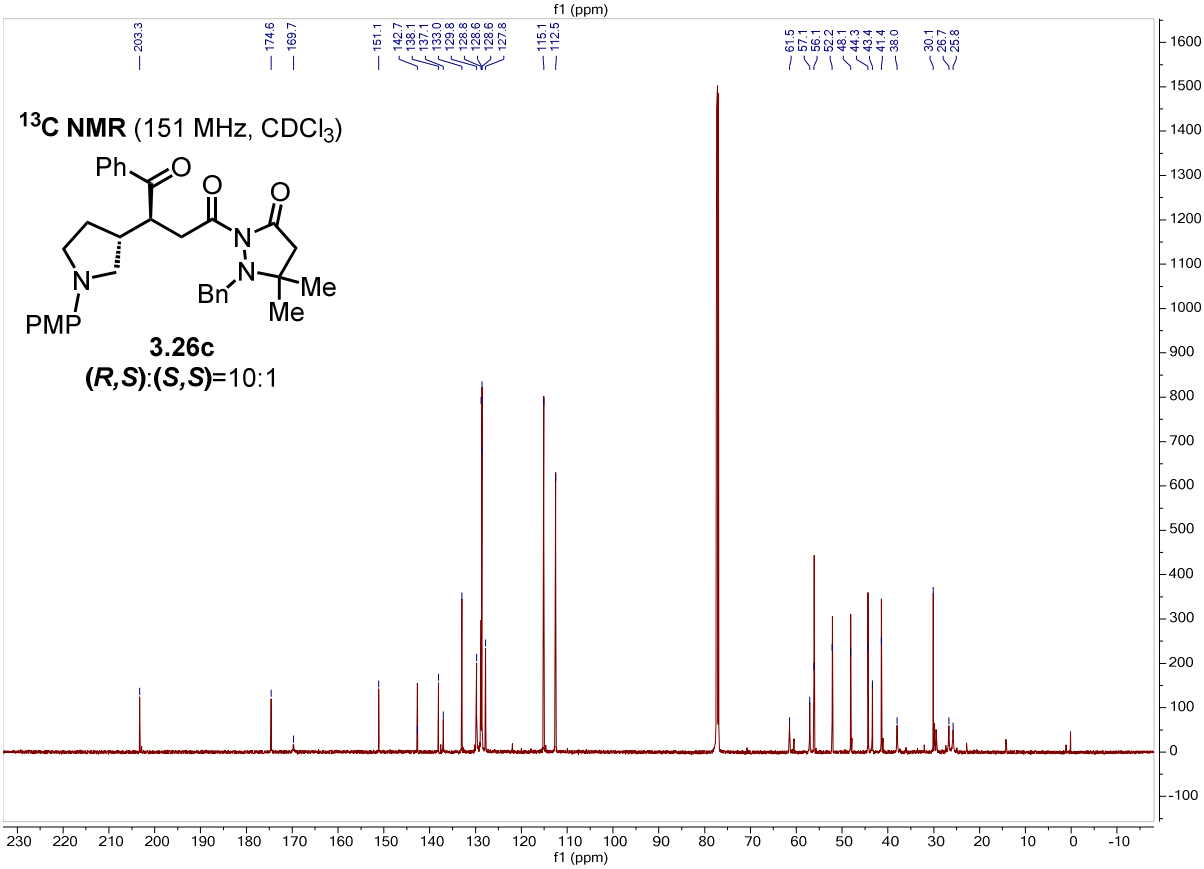
3.26b-(*R,S*)

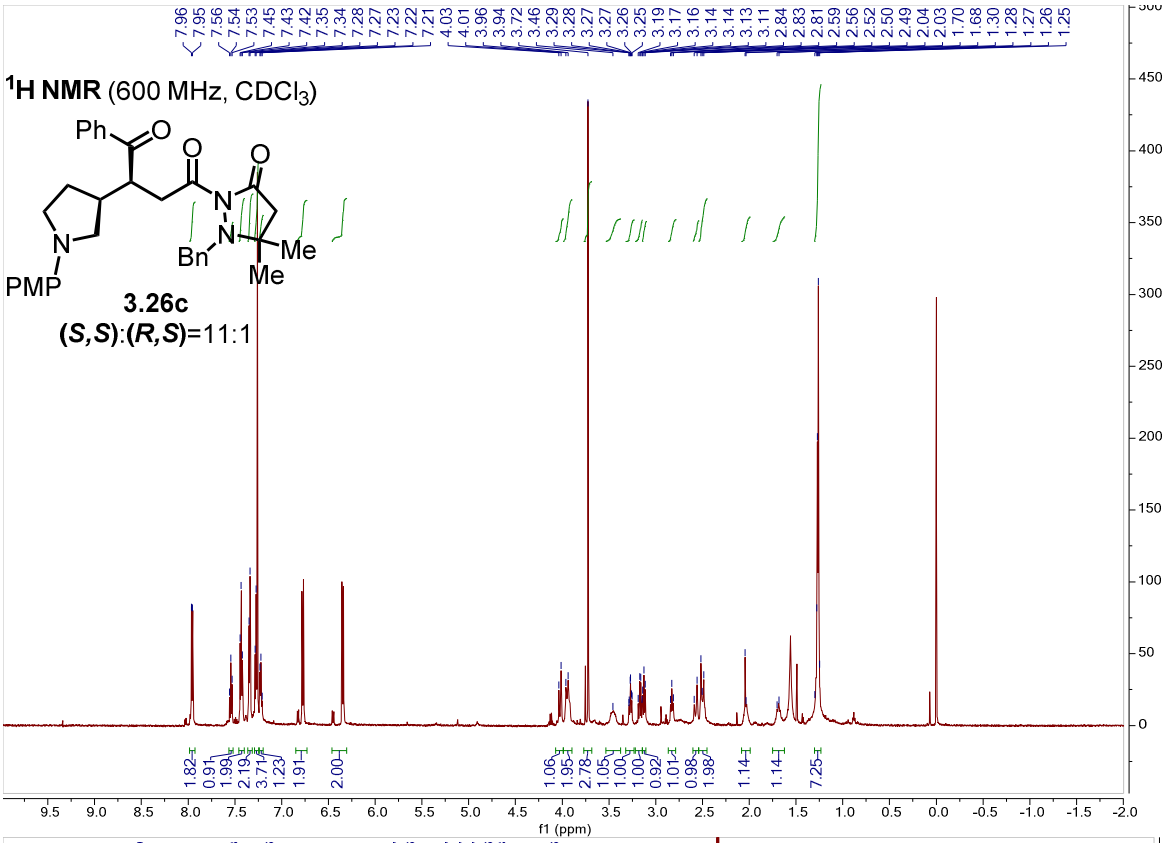

174.6
174.2
169.1
151.1
142.8
137.3
129.6
128.6
127.8
115.2
112.6
61.4
60.8
57.0
56.1
52.3
48.1
44.0
43.6
40.8
37.5
29.8
29.7
26.5
26.0
14.4
f1 (ppm)

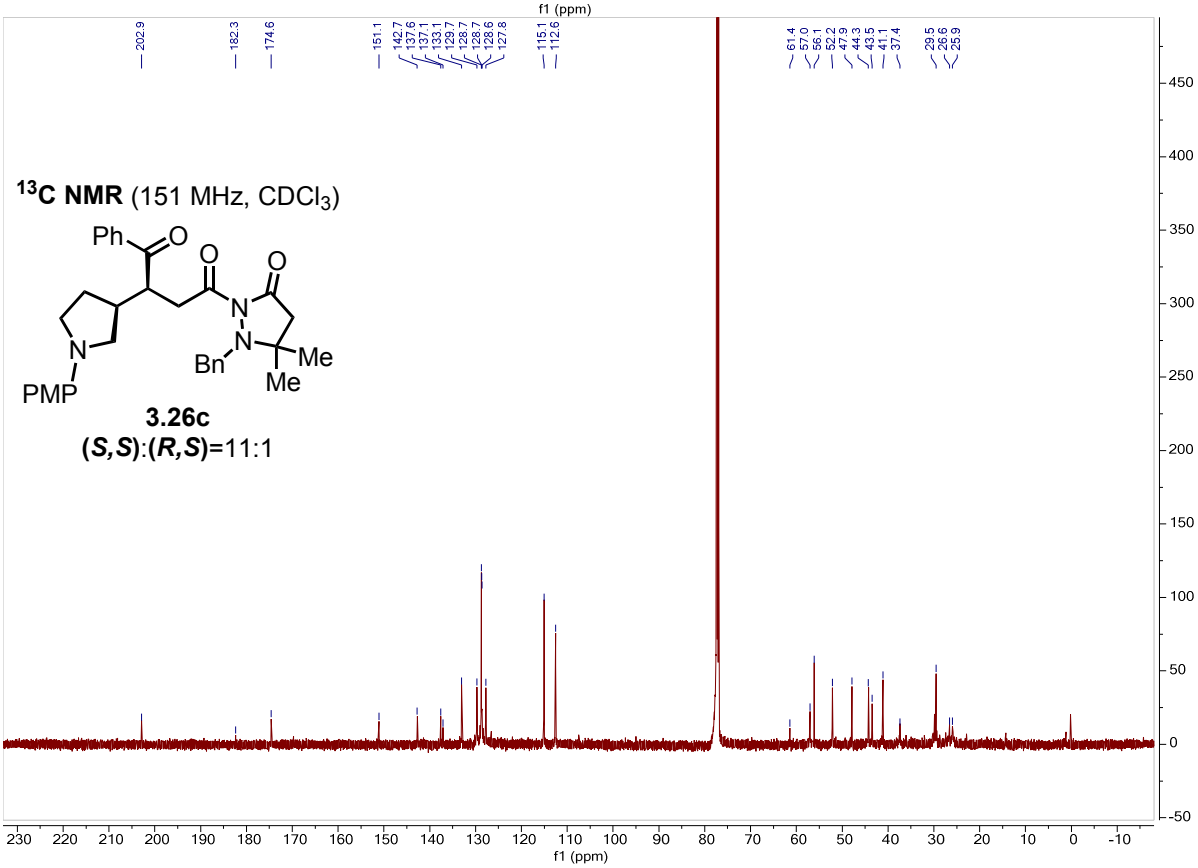

^{1}H NMR (600 MHz, CDCl$_3$)
EtO
O
O
O
N
N
Bn
Me
Me
N
PMP
3.26b
mixture of diatereomers
(R,S):(S,S) = 2.3:1
f1 (ppm)


^{13}C NMR (151 MHz, CDCl$_3$)
EtO
O
O
O
N
N
Bn
Me
Me
N
PMP
3.26b
mixture of diatereomers
(R,S):(S,S) = 2.3:1
f1 (ppm)

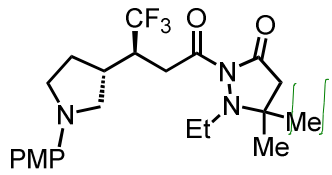

^{1}H NMR (600 MHz, $CDCl_3$)
Ph
O
O
O
N
N
Bn
Me
Me
N
PMP
3.26c
(*R,S*):(*S,S*)=10:1
f1 (ppm)


^{13}C NMR (151 MHz, $CDCl_3$)
Ph
O
O
O
N
N
Bn
Me
Me
N
PMP
3.26c
(*R,S*):(*S,S*)=10:1
f1 (ppm)


1H NMR (600 MHz, CDCl3)
Ph
O
O
O
N
N
Bn
Me
Me
N
PMP
3.26c
(S,S):(R,S)=11:1
f1 (ppm)

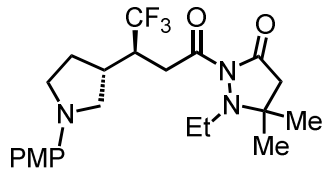

13C NMR (151 MHz, CDCl3)
Ph
O
O
O
N
N
Bn
Me
Me
N
PMP
3.26c
(S,S):(R,S)=11:1
f1 (ppm)

^{1}H NMR (500 MHz, $CDCl_3$)

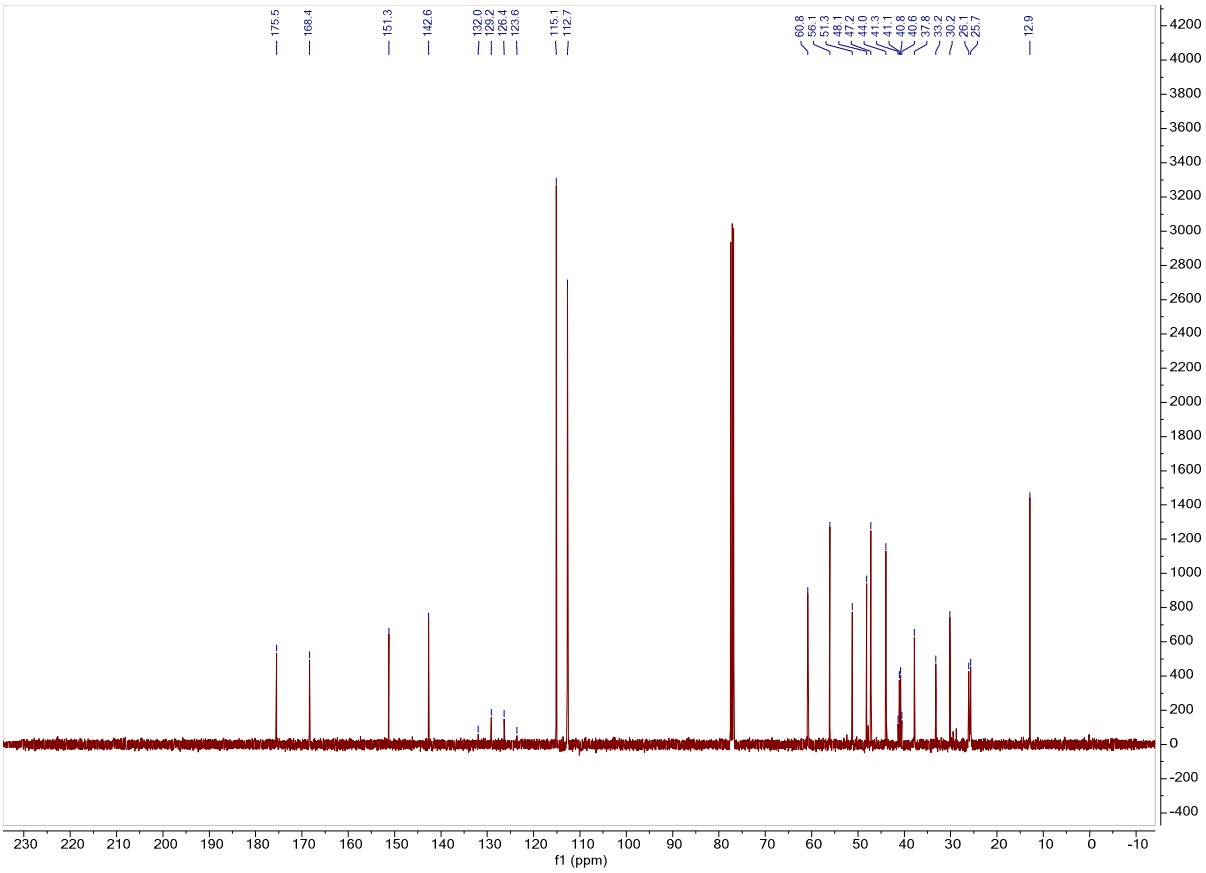


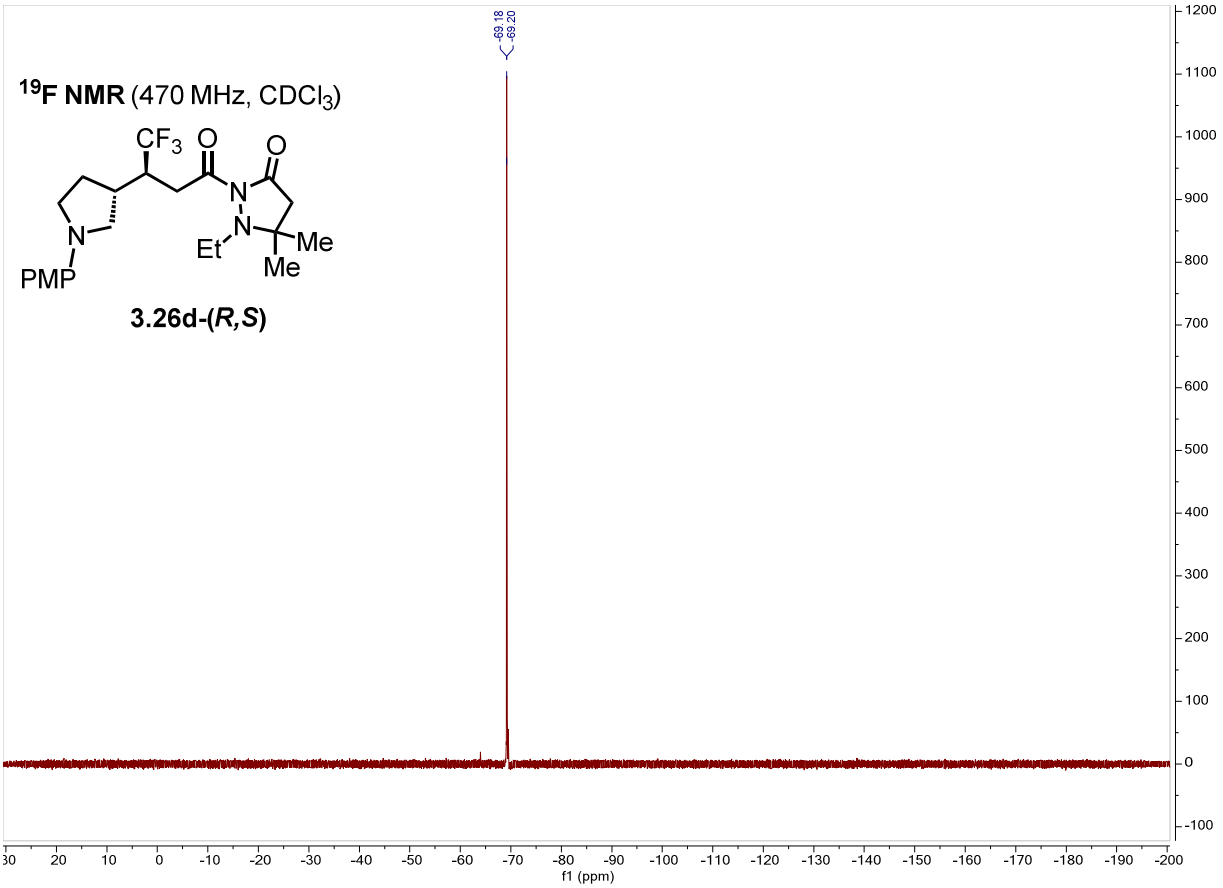
3.26d-(*R,S*)

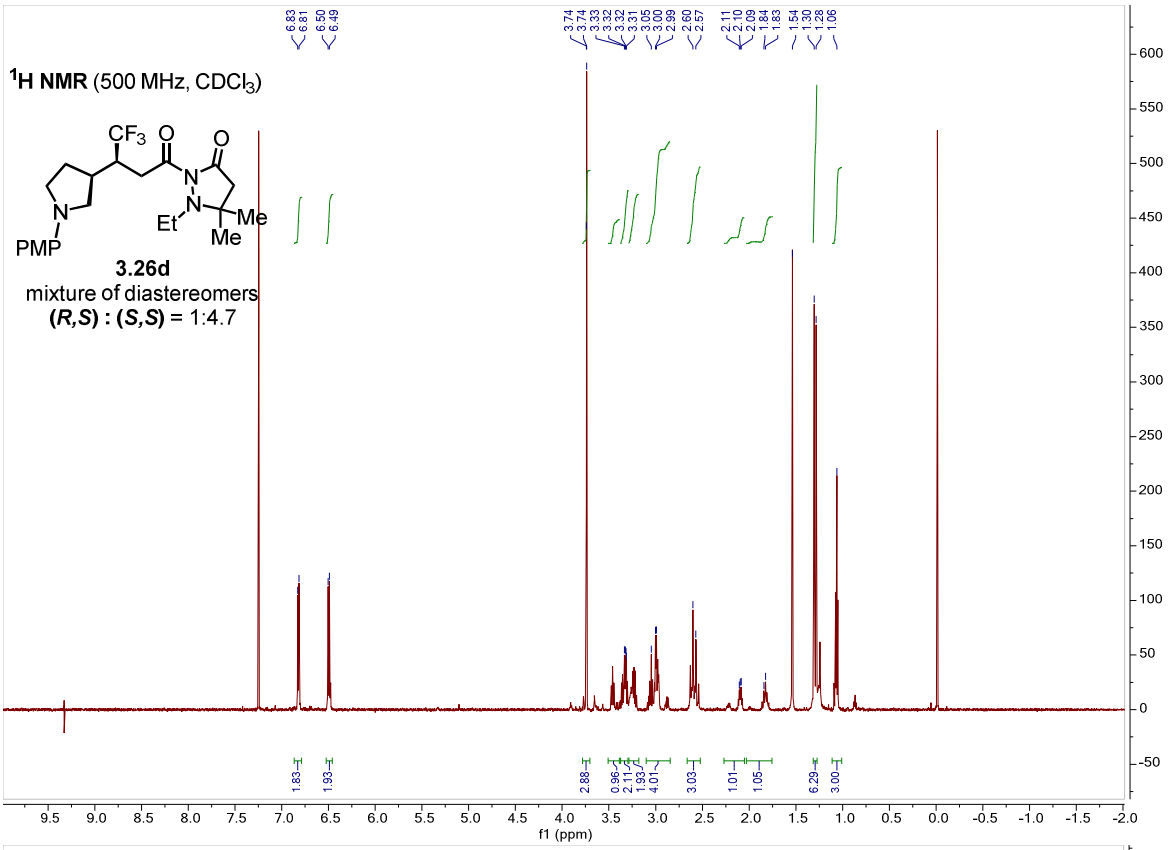
^{13}C NMR (101 MHz, $CDCl_3$)

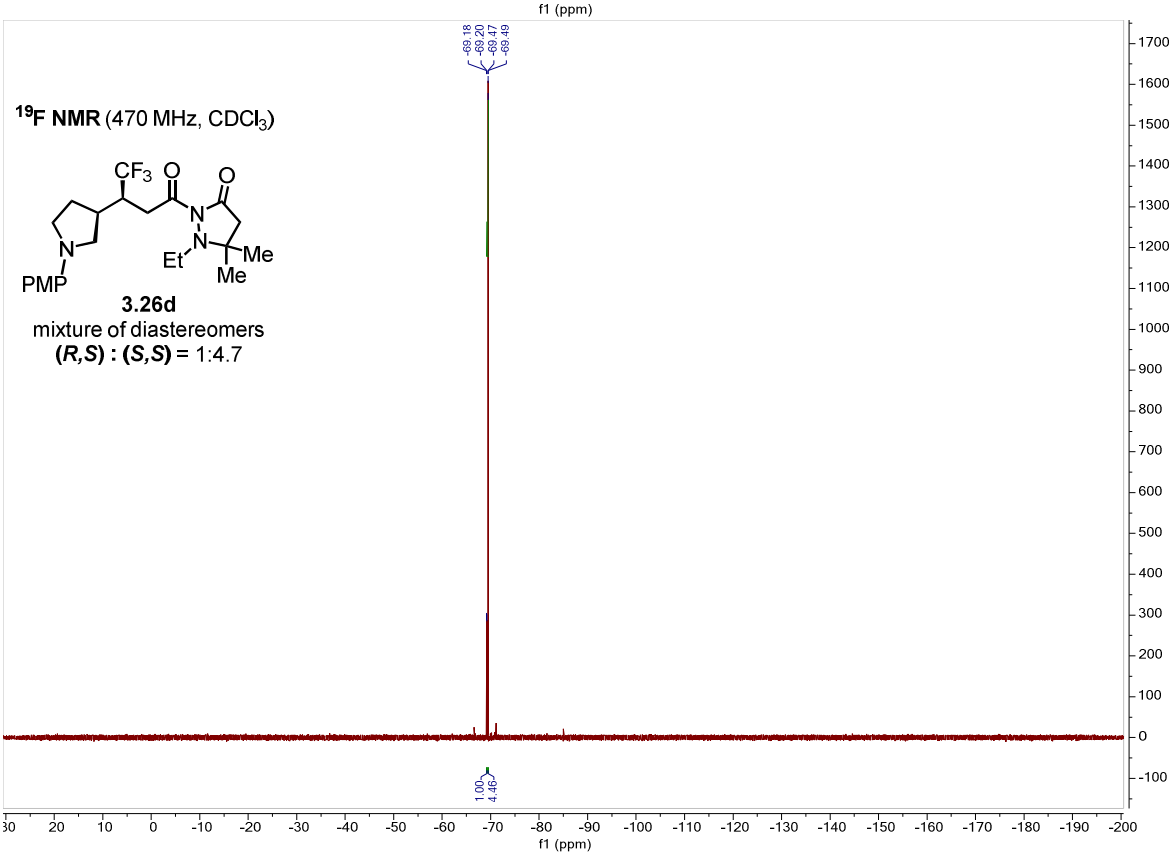


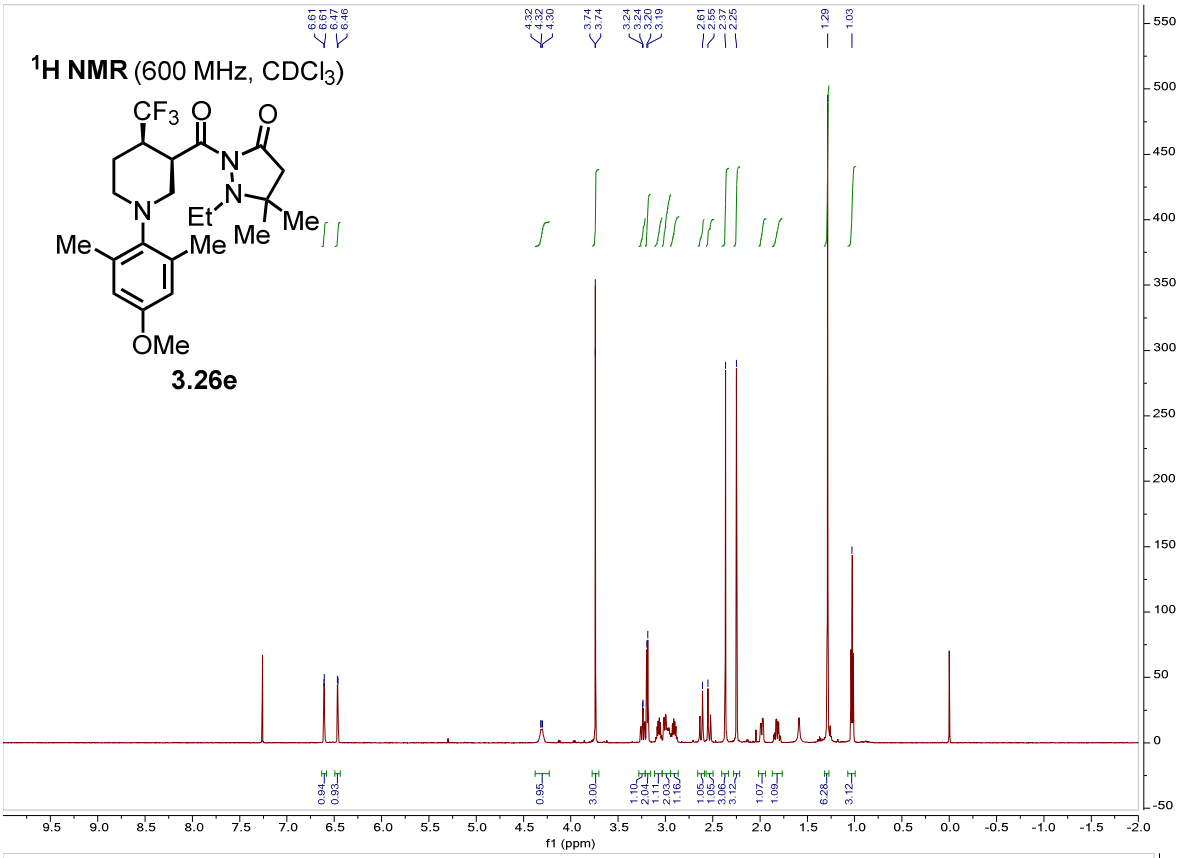
3.26d-(*R,S*)

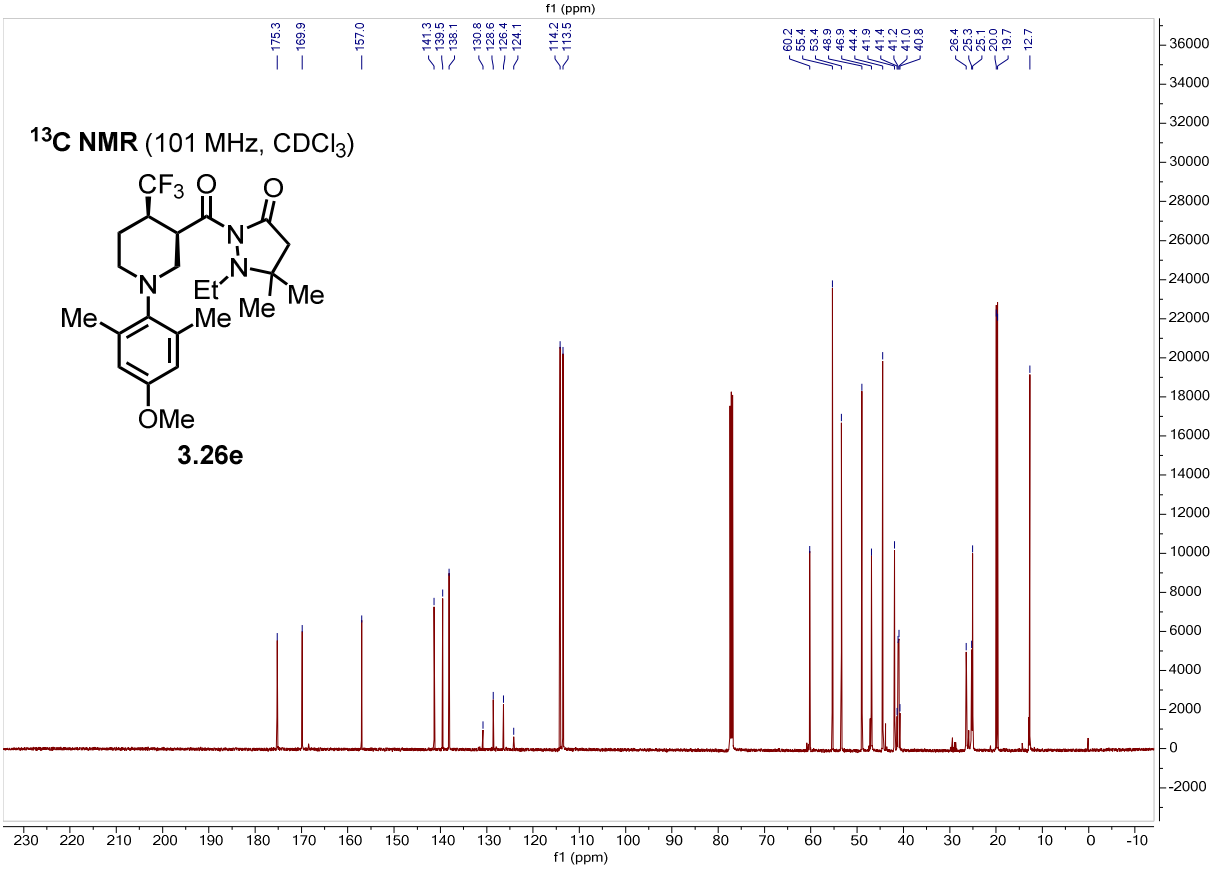

175.5
168.4
151.3
142.6
132.0
129.2
126.4
123.6
115.1
112.7
60.8
56.1
51.3
48.1
47.2
44.0
41.3
41.1
40.8
40.6
37.8
33.2
30.2
26.1
25.7
12.9
f1 (ppm)

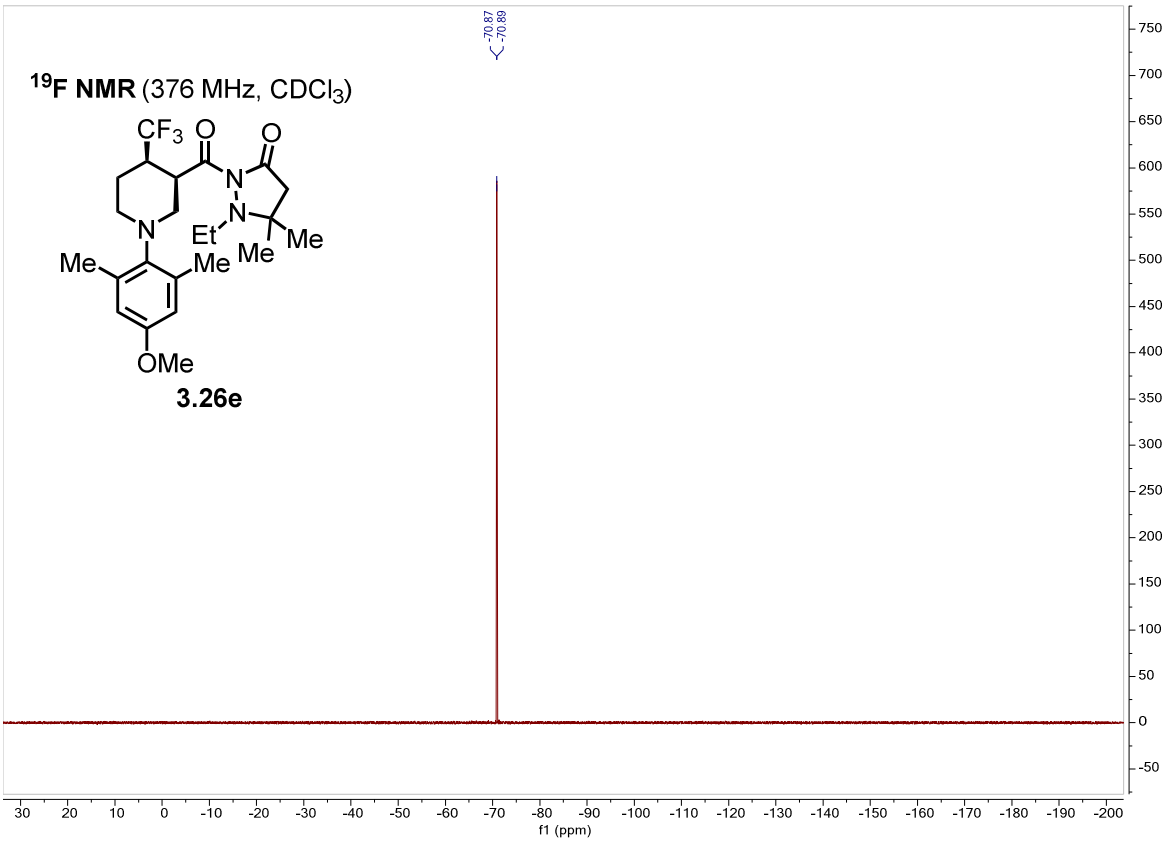

19F NMR (470 MHz, CDCl3)
CF3
O
O
N
N
Et
Me
Me
PMP
3.26d-(R,S)
-69.18
-69.20
f1 (ppm)

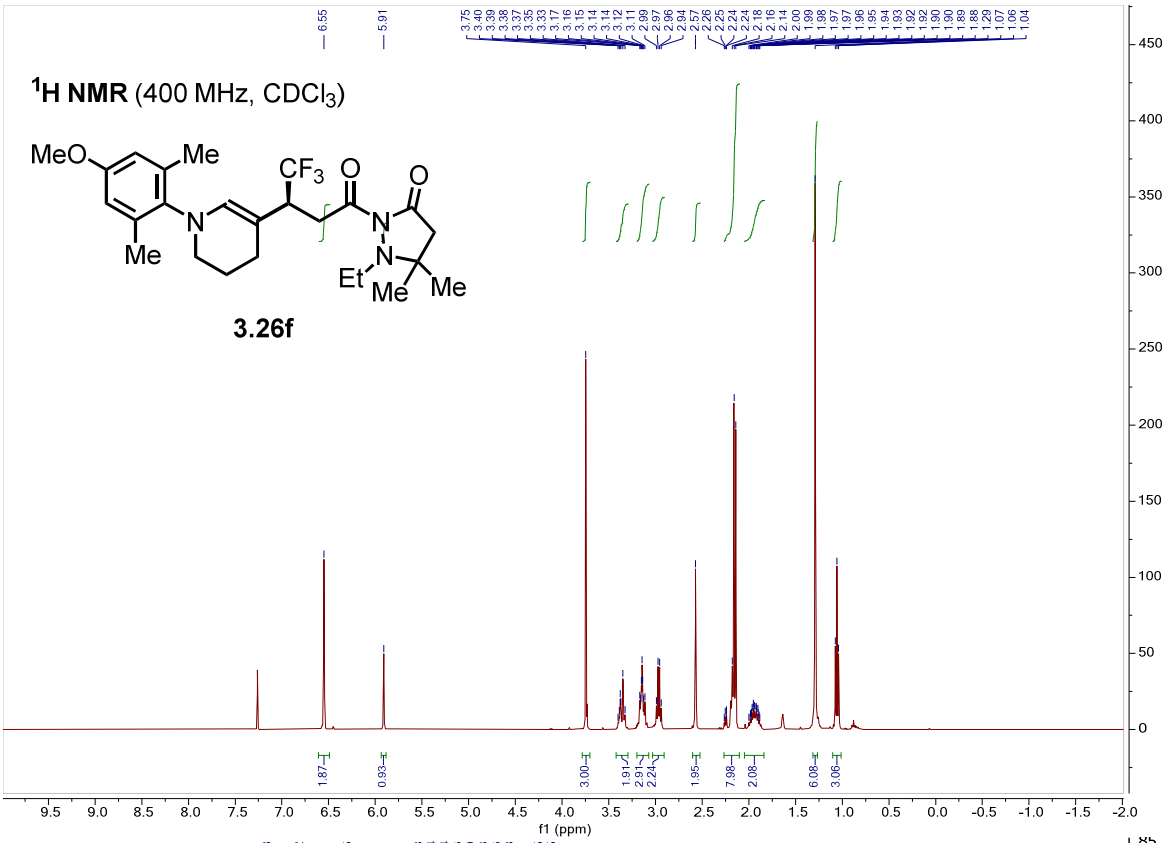

^{1}H NMR (500 MHz, $CDCl_3$)
CF_3 O O
N N
Et Me
Me
PMP
3.26d
mixture of diastereomers
(R,S) : (S,S) = 1:4.7
f1 (ppm)

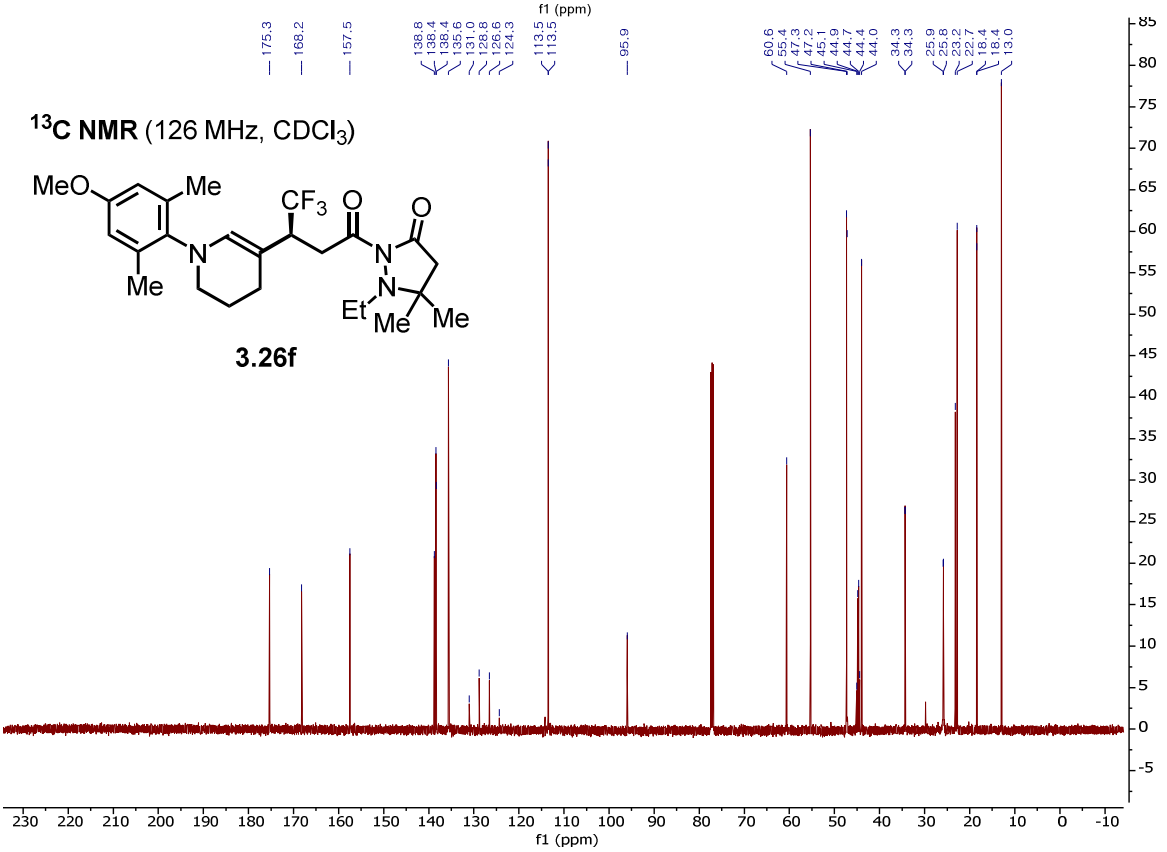

^{19}F NMR (470 MHz, $CDCl_3$)
CF_3 O O
N N
Et Me
Me
PMP
3.26d
mixture of diastereomers
(R,S) : (S,S) = 1:4.7
f1 (ppm)

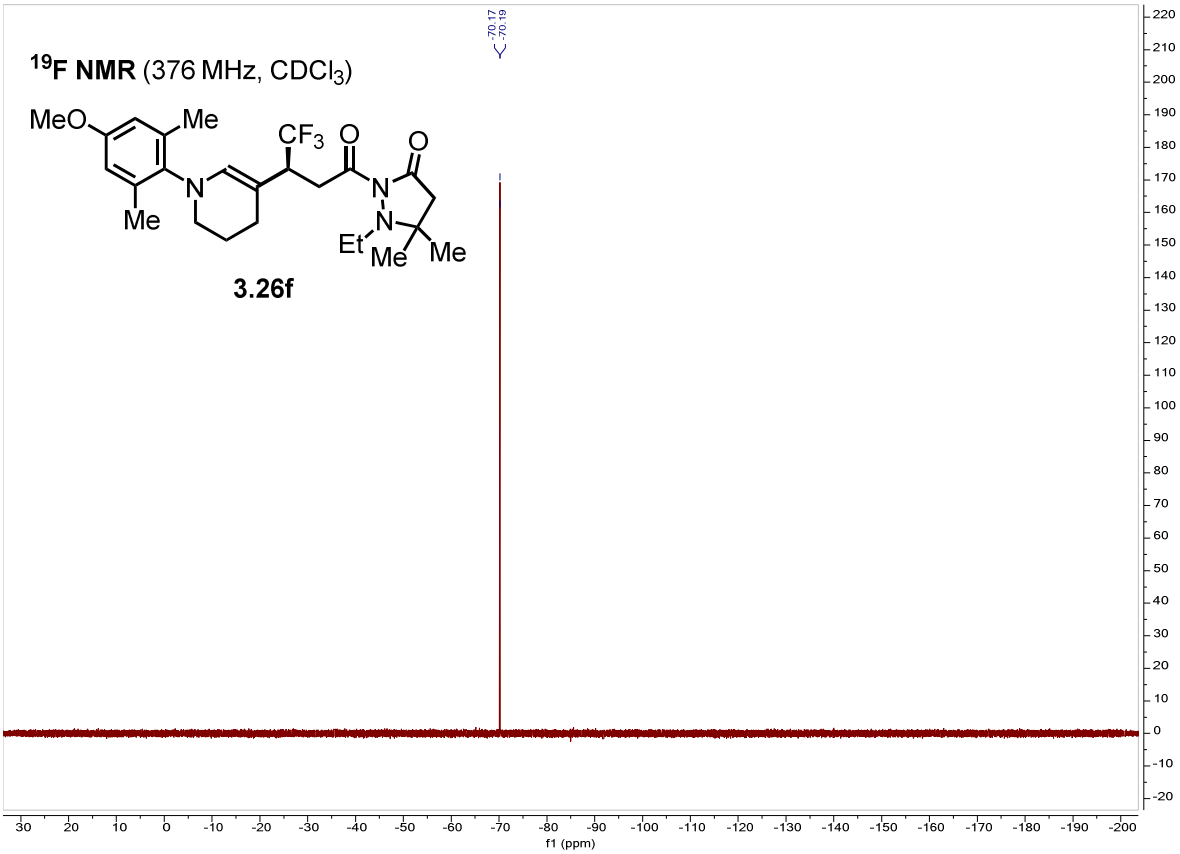

1H NMR (600 MHz, CDCl3)
CF3
O
O
N
N
Et
Me
Me
Me
Me
N
OMe
3.26e
f1 (ppm)

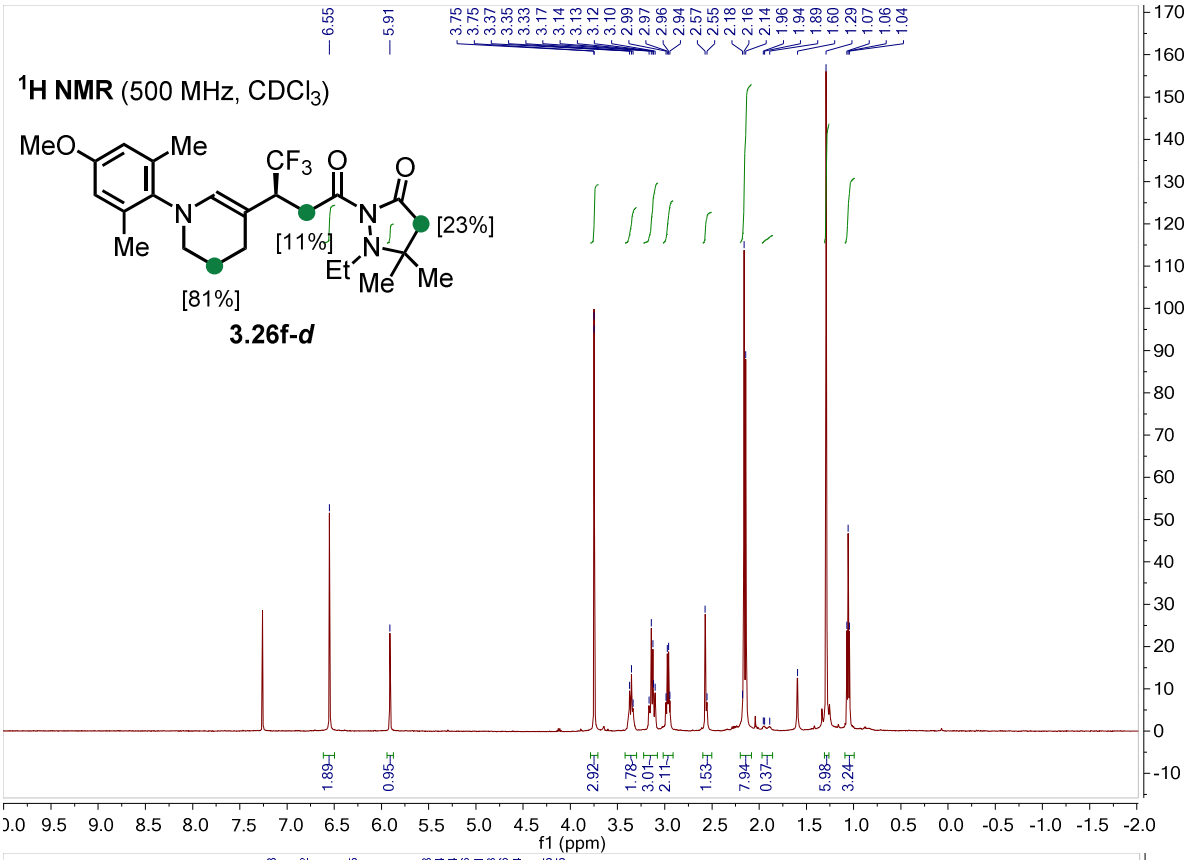

13C NMR (101 MHz, CDCl3)
CF3
O
O
N
N
Et
Me
Me
Me
Me
N
OMe
3.26e
f1 (ppm)

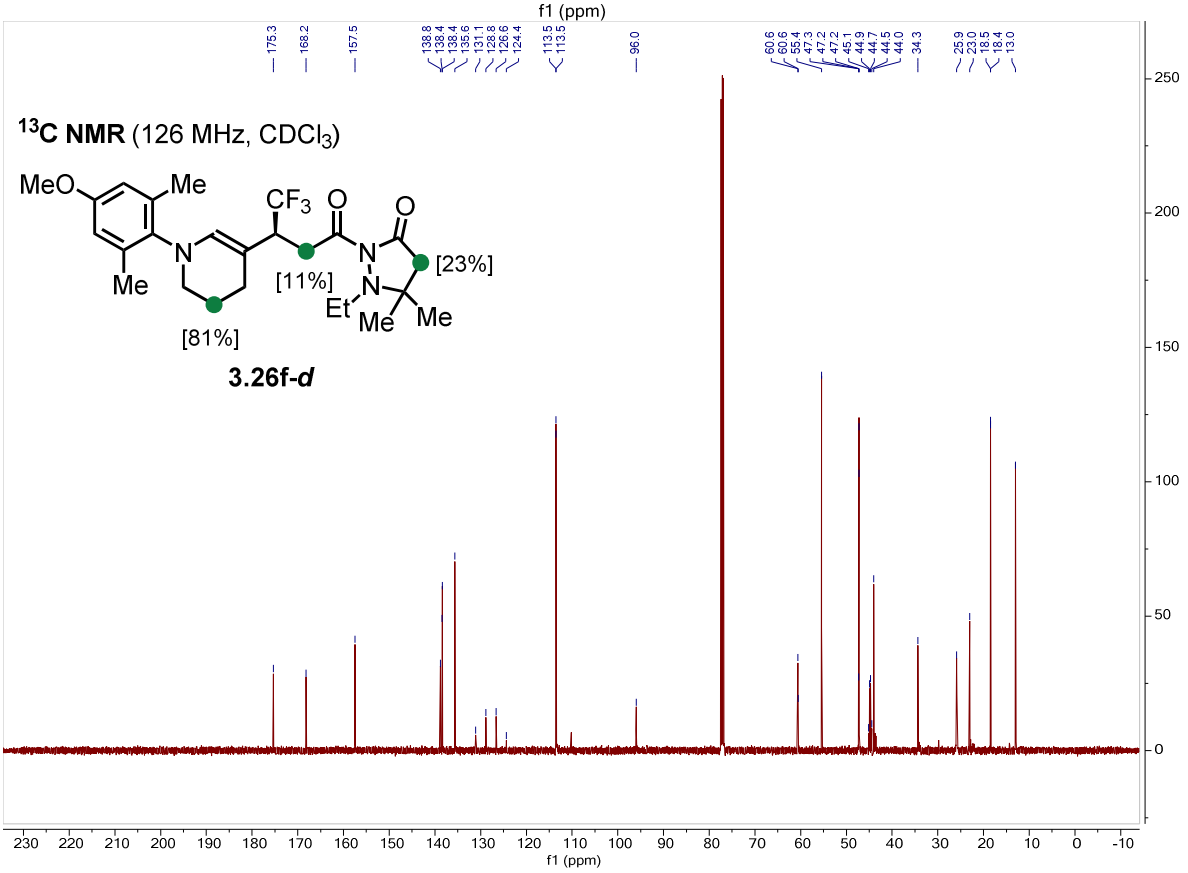

19F NMR (376 MHz, CDCl3)
CF3
O
O
N
N
Et
Me
Me
Me
Me
N
OMe
3.26e
-70.87
-70.89
f1 (ppm)

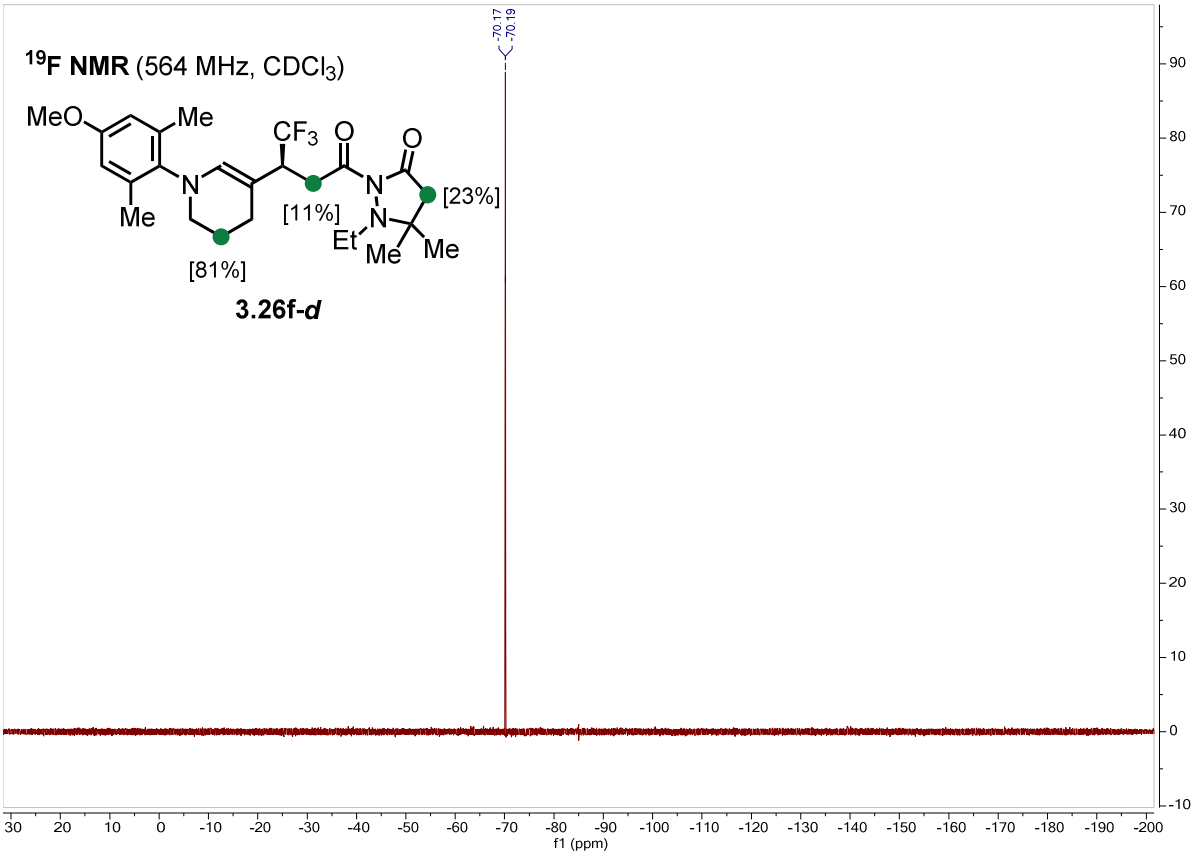

^{1}H NMR (400 MHz, $CDCl_3$)
MeO
Me
Me
CF3
O
O
N
N
N
Et
Me
Me
3.26f
f1 (ppm)

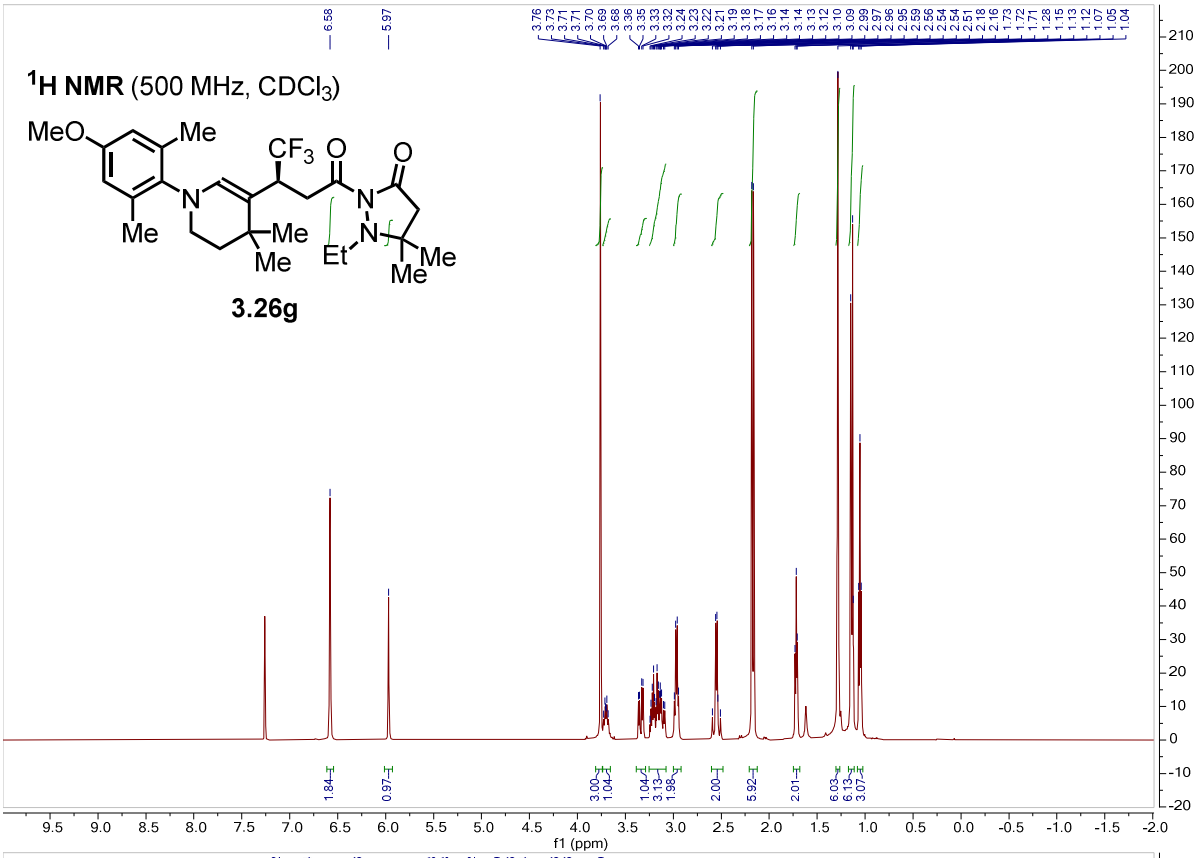

^{13}C NMR (126 MHz, $CDCl_3$)
MeO
Me
Me
CF3
O
O
N
N
N
Et
Me
Me
3.26f
f1 (ppm)

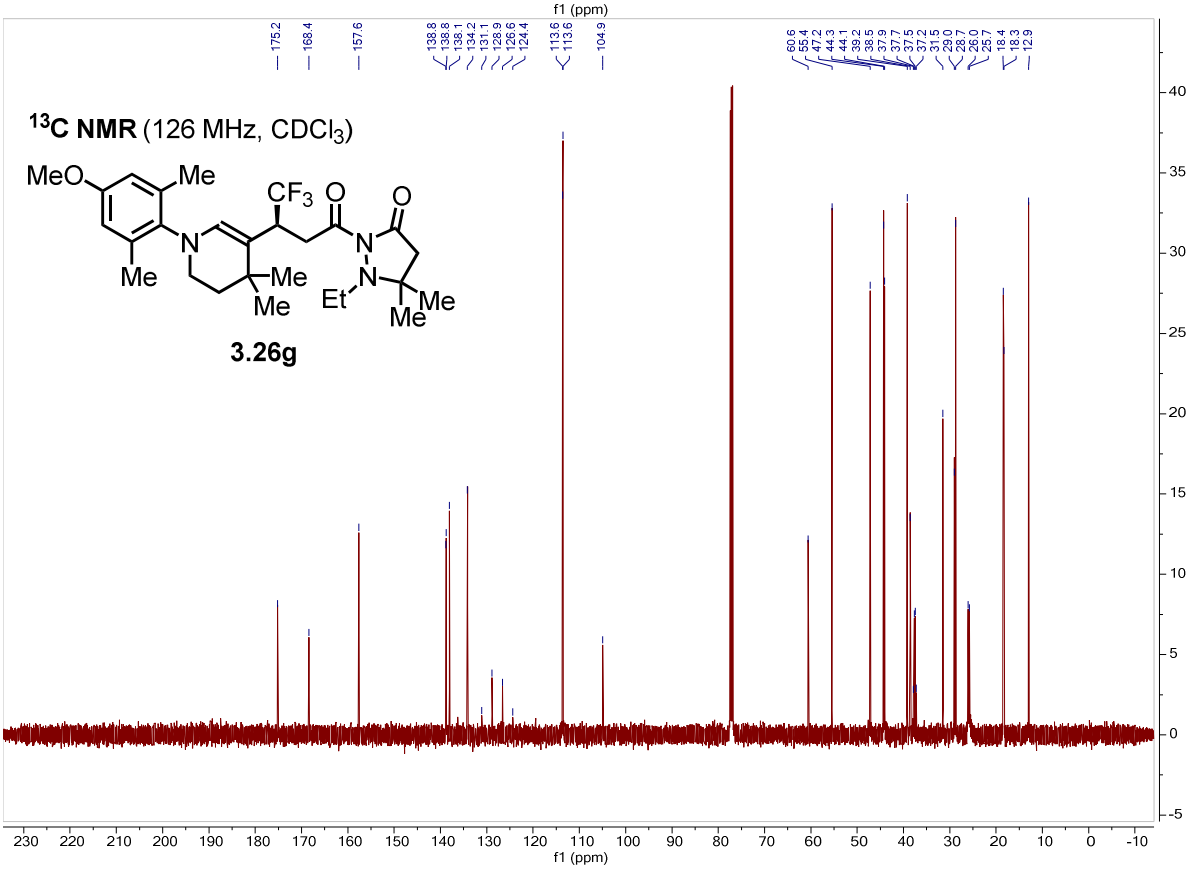

19F NMR (376 MHz, CDCl3)
MeO
Me
Me
CF3
O
O
N
N
N
Et
Me
Me
3.26f
-70.17
-70.19
f1 (ppm)

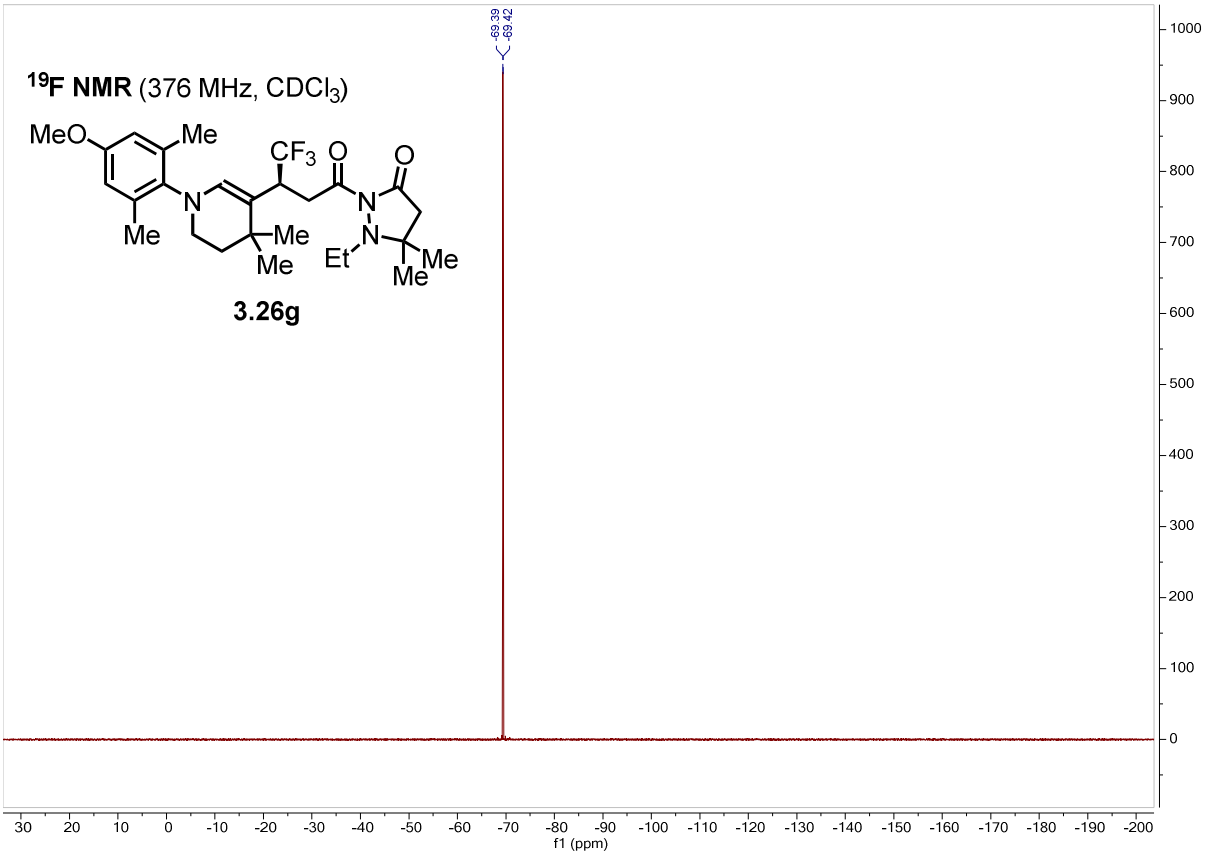

^{1}H NMR (500 MHz, CDCl$_3$)
MeO
Me
CF$_3$
O
O
N
N
N
Et
Me
Me
Me
[81%]
[11%]
[23%]
3.26f-*d*
f1 (ppm)

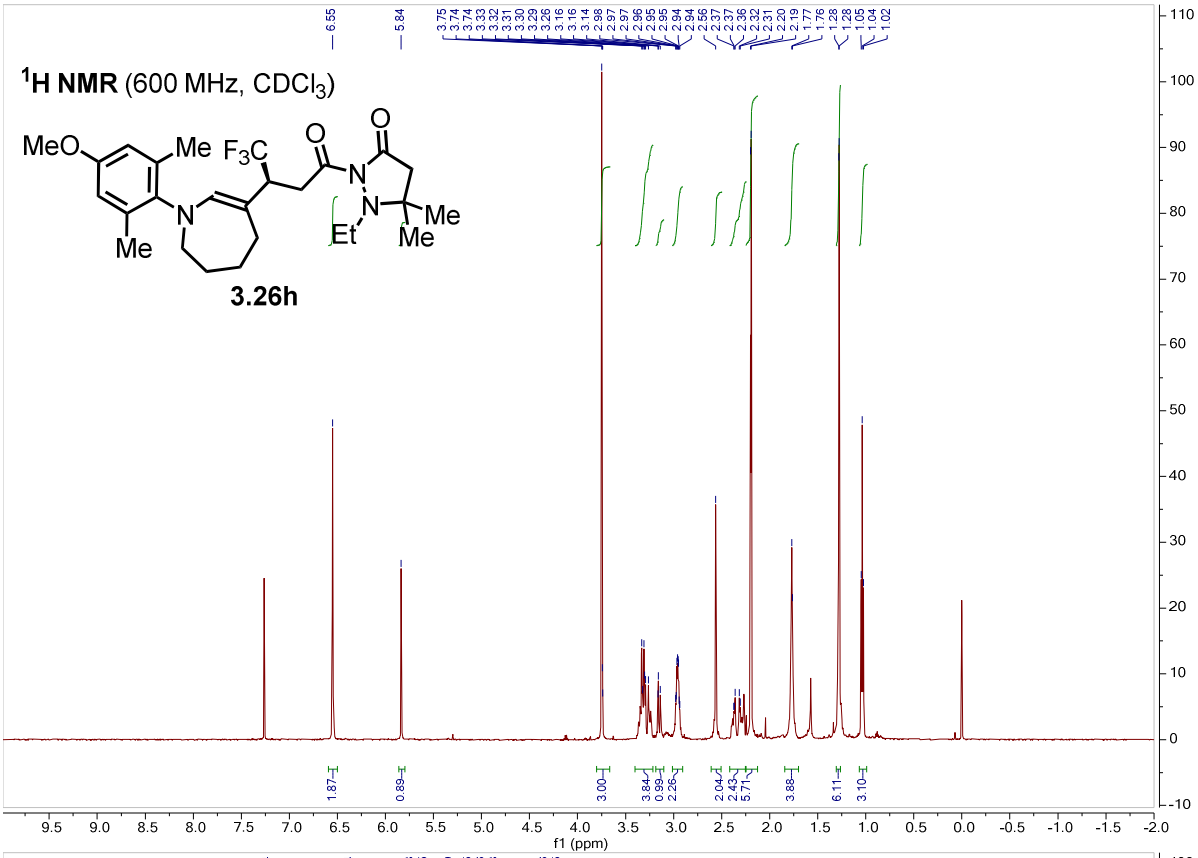

^{13}C NMR (126 MHz, CDCl$_3$)
MeO
Me
CF$_3$
O
O
N
N
N
Et
Me
Me
Me
[81%]
[11%]
[23%]
3.26f-*d*
f1 (ppm)

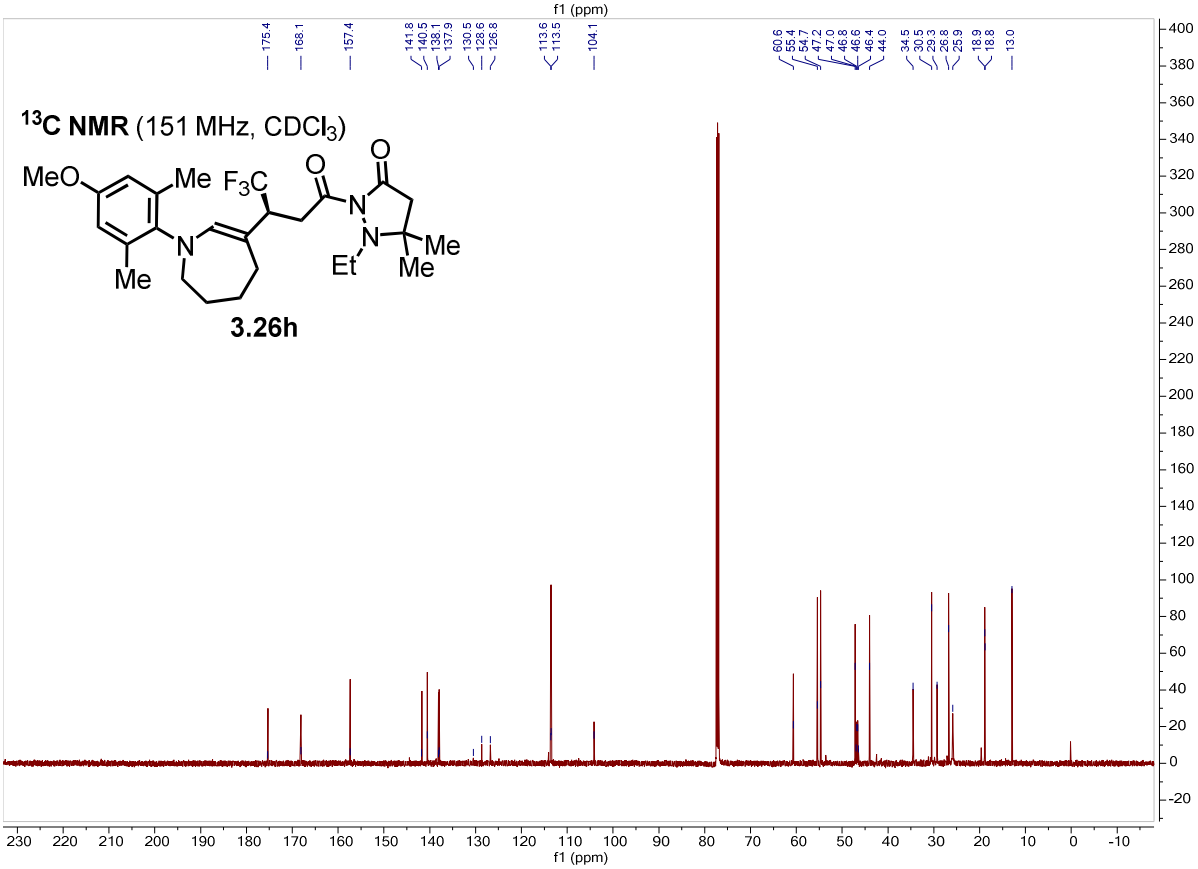

19F NMR (564 MHz, CDCl3)
MeO
Me
Me
N
CF3
O
O
N
N
[23%]
[11%]
Et
Me
Me
[81%]
3.26f-d
-70.17
-70.19
90
80
70
60
50
40
30
20
10
0
-10
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

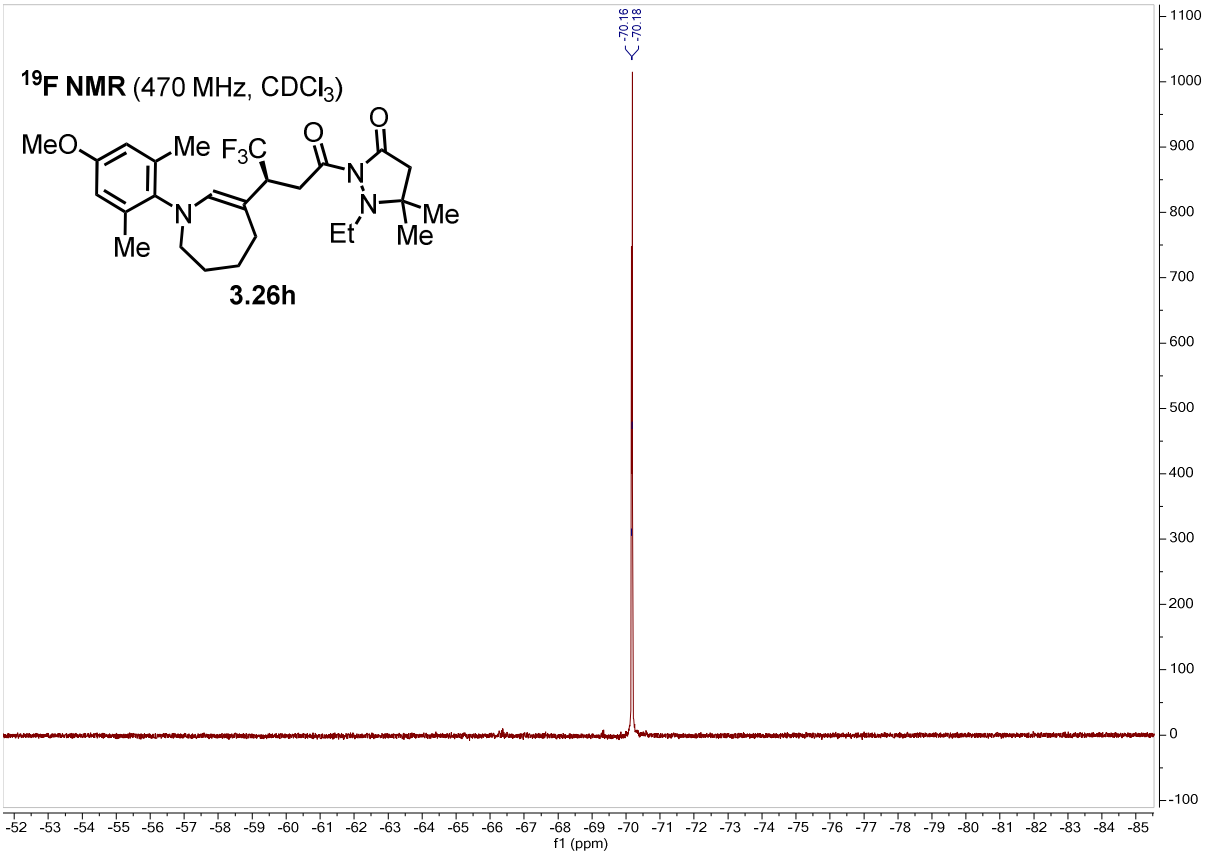

^{1}H NMR (500 MHz, CDCl$_3$)
MeO
Me
CF$_3$
O
O
N
N
N
Me
Me
Me
Et
Me
3.26g
f1 (ppm)

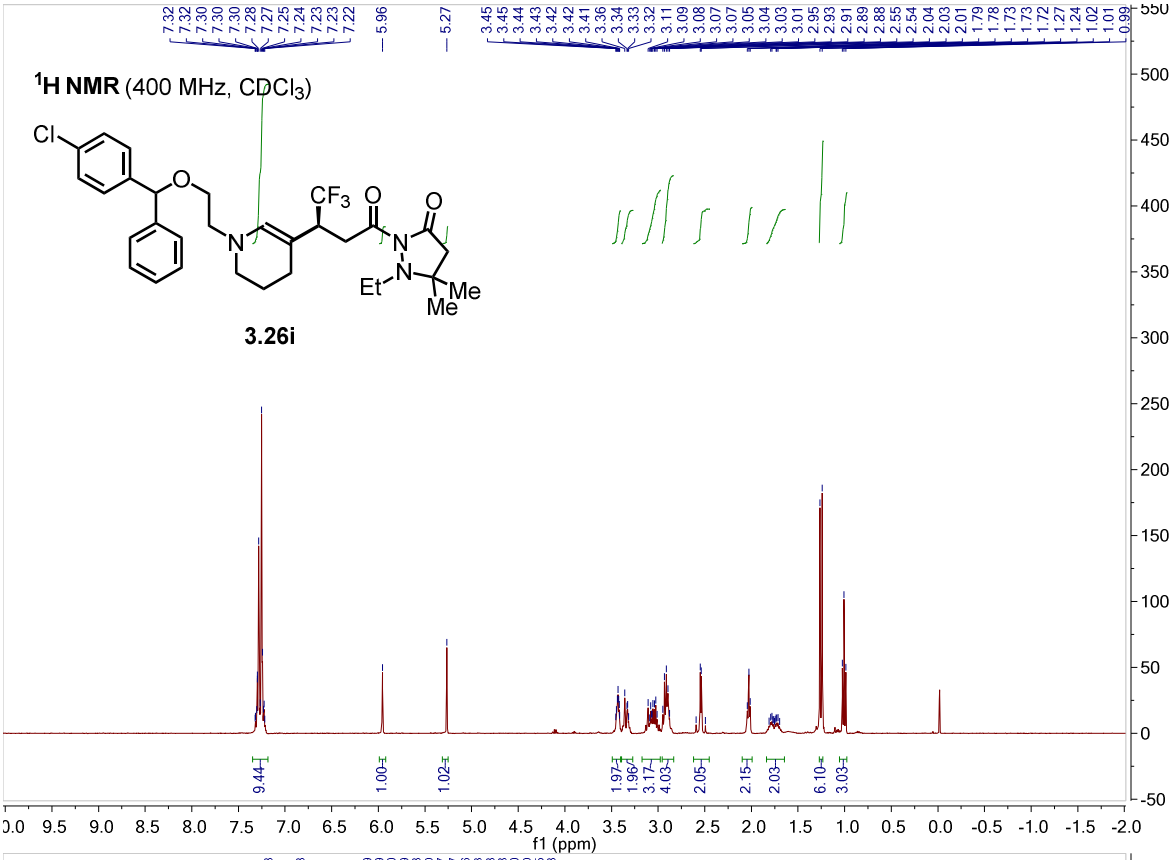

^{13}C NMR (126 MHz, CDCl$_3$)
MeO
Me
CF$_3$
O
O
N
N
N
Me
Me
Me
Et
Me
3.26g
f1 (ppm)

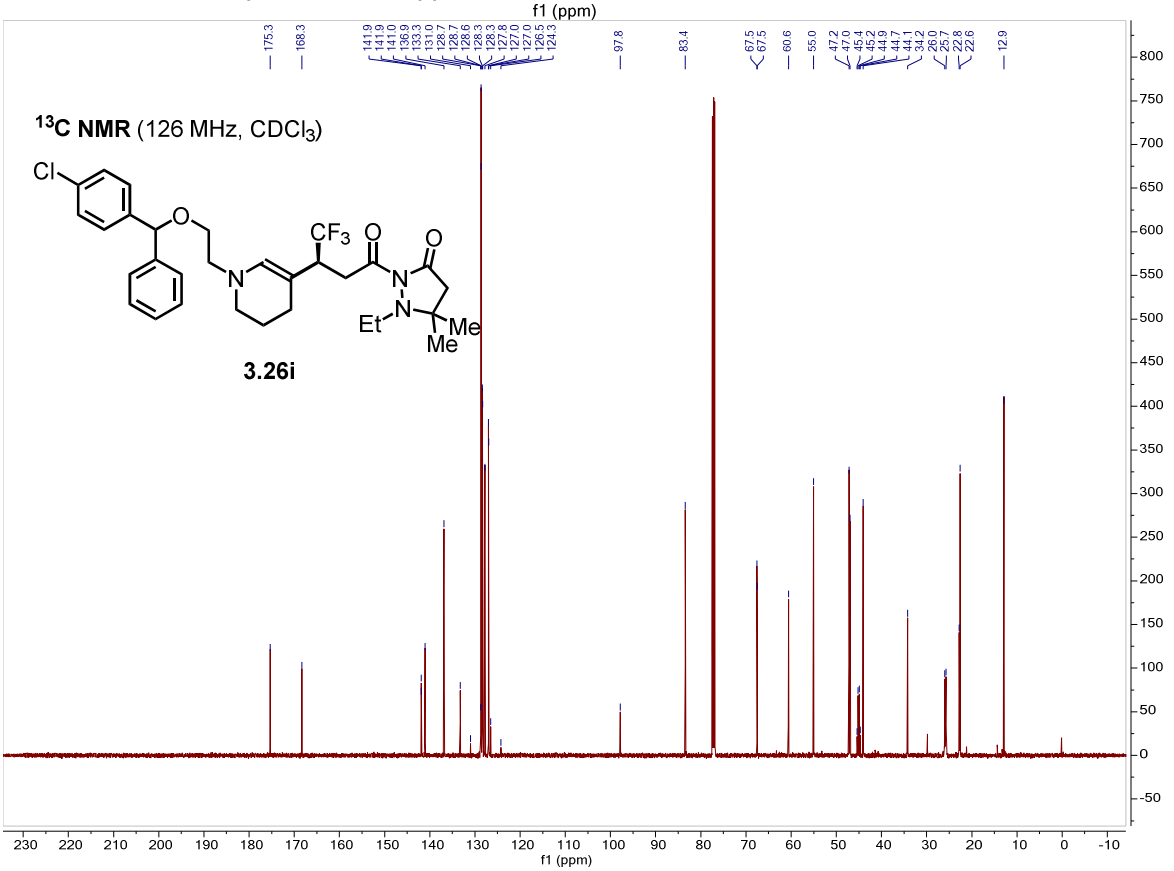

-69.39
-69.42
19F NMR (376 MHz, CDCl3)
MeO
Me
CF3
O
O
N
N
N
Me
Me
Me
Et
Me
Me
3.26g
1000
900
800
700
600
500
400
300
200
100
0
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

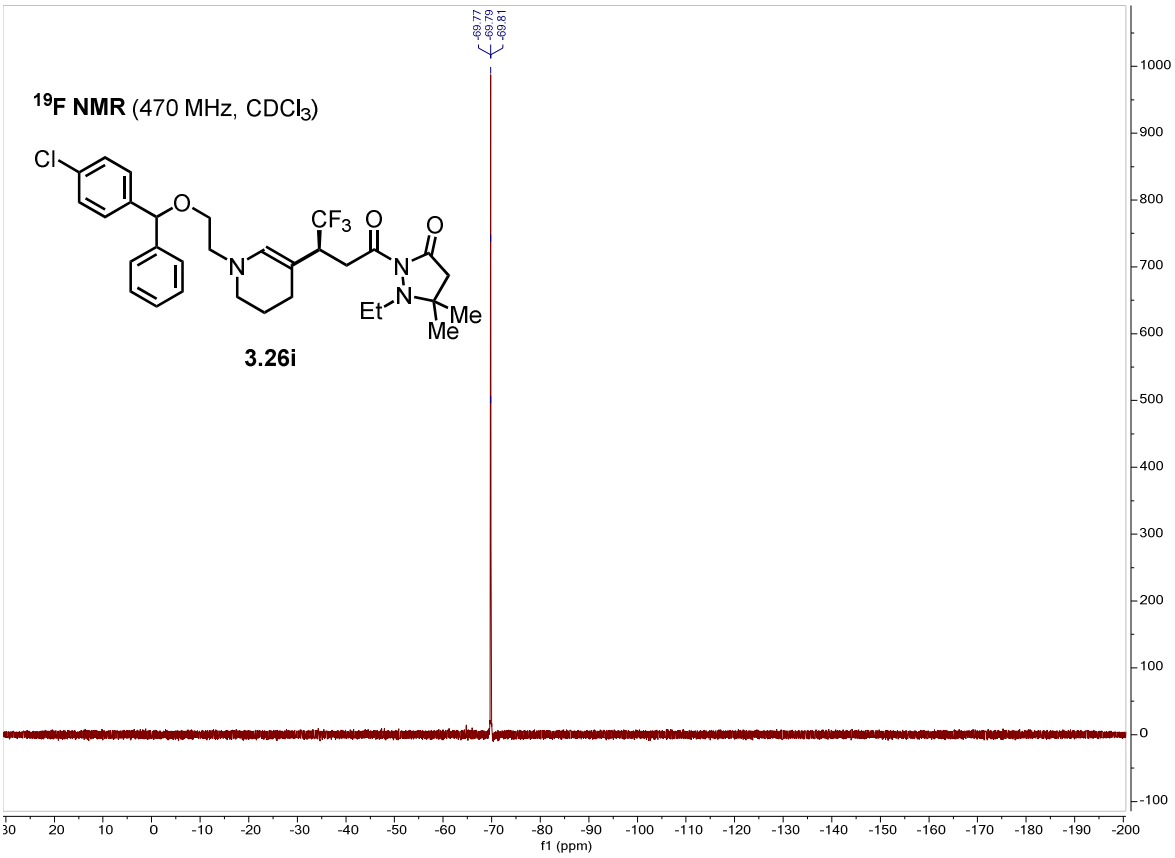

1H NMR (600 MHz, CDCl3)
MeO
Me
F3C
O
N
N
Et
Me
Me
Me
3.26h
f1 (ppm)

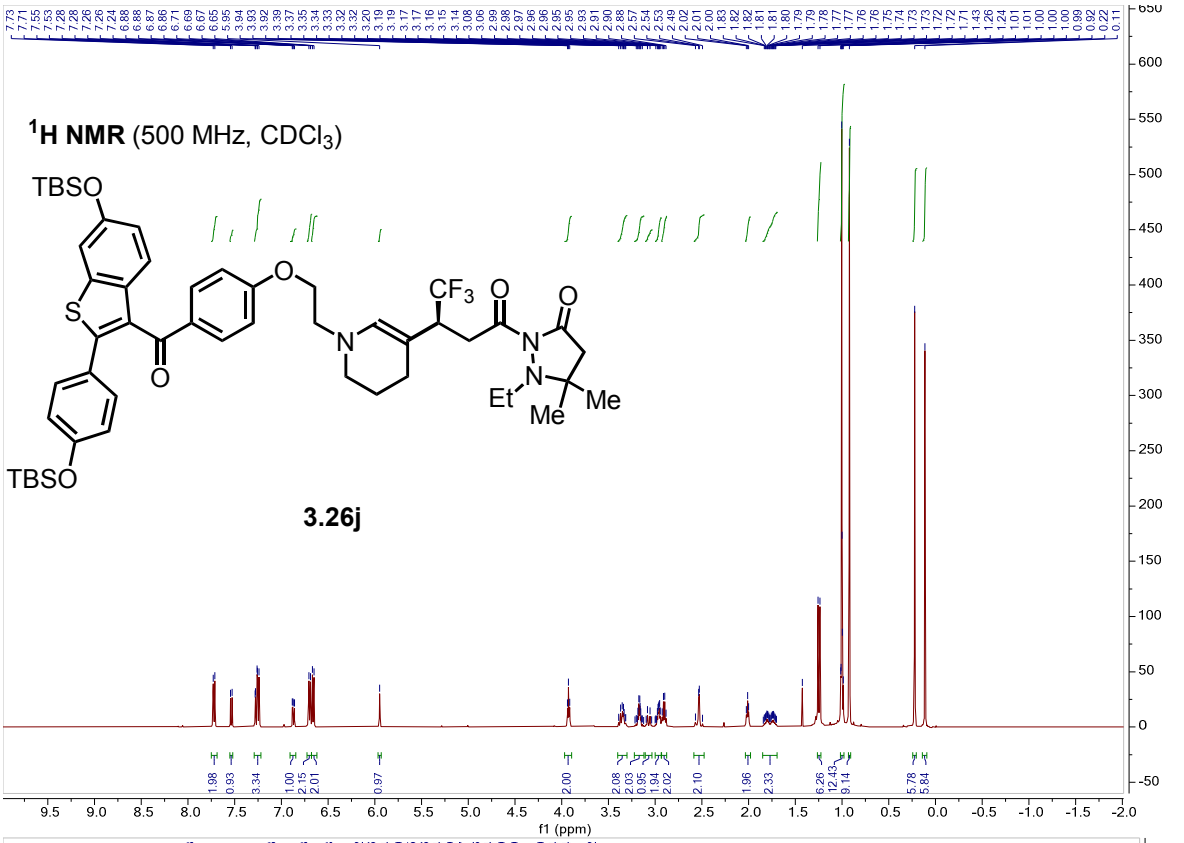

13C NMR (151 MHz, CDCl3)
MeO
Me
F3C
O
N
N
Et
Me
Me
Me
3.26h
f1 (ppm)

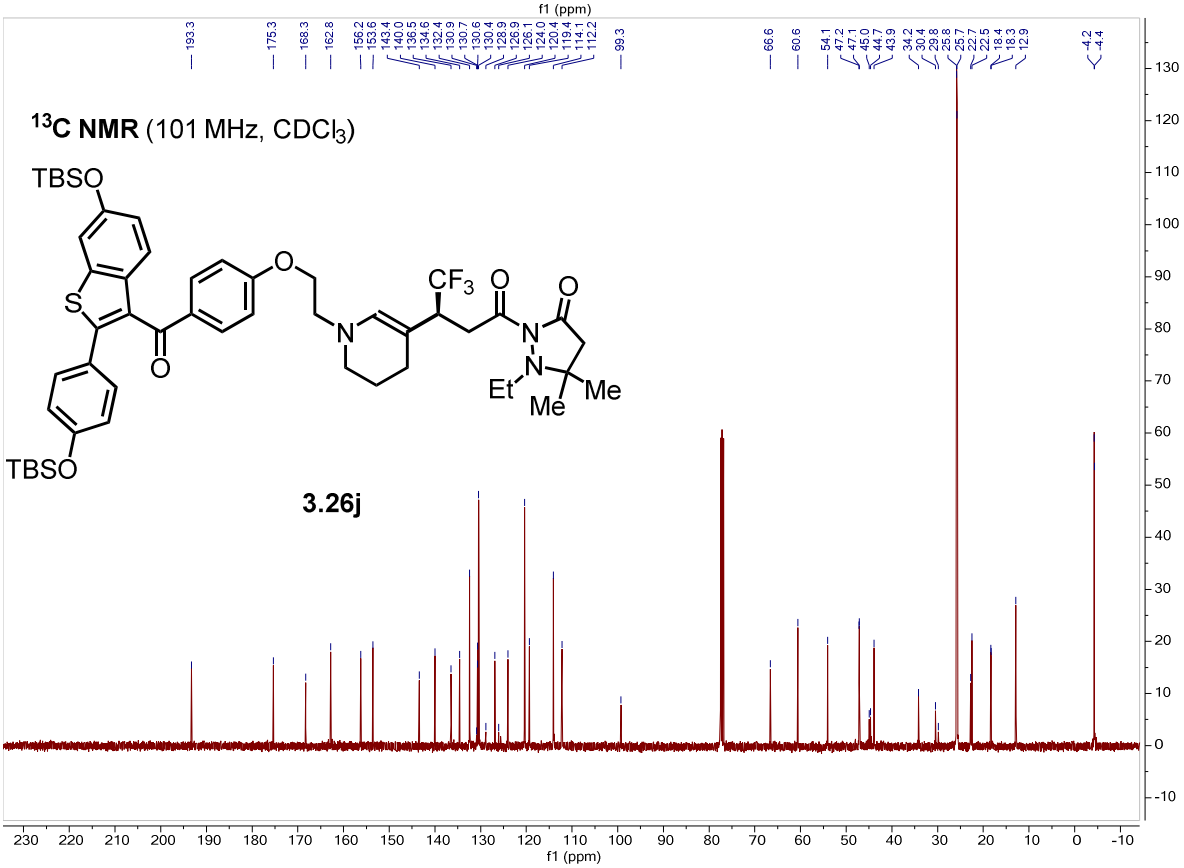

19F NMR (470 MHz, CDCl3)
MeO
Me
F3C
O
O
N
N
Et
Me
Me
N
Me
3.26h
-70.16
-70.18
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-52 -53 -54 -55 -56 -57 -58 -59 -60 -61 -62 -63 -64 -65 -66 -67 -68 -69 -70 -71 -72 -73 -74 -75 -76 -77 -78 -79 -80 -81 -82 -83 -84 -85
f1 (ppm)

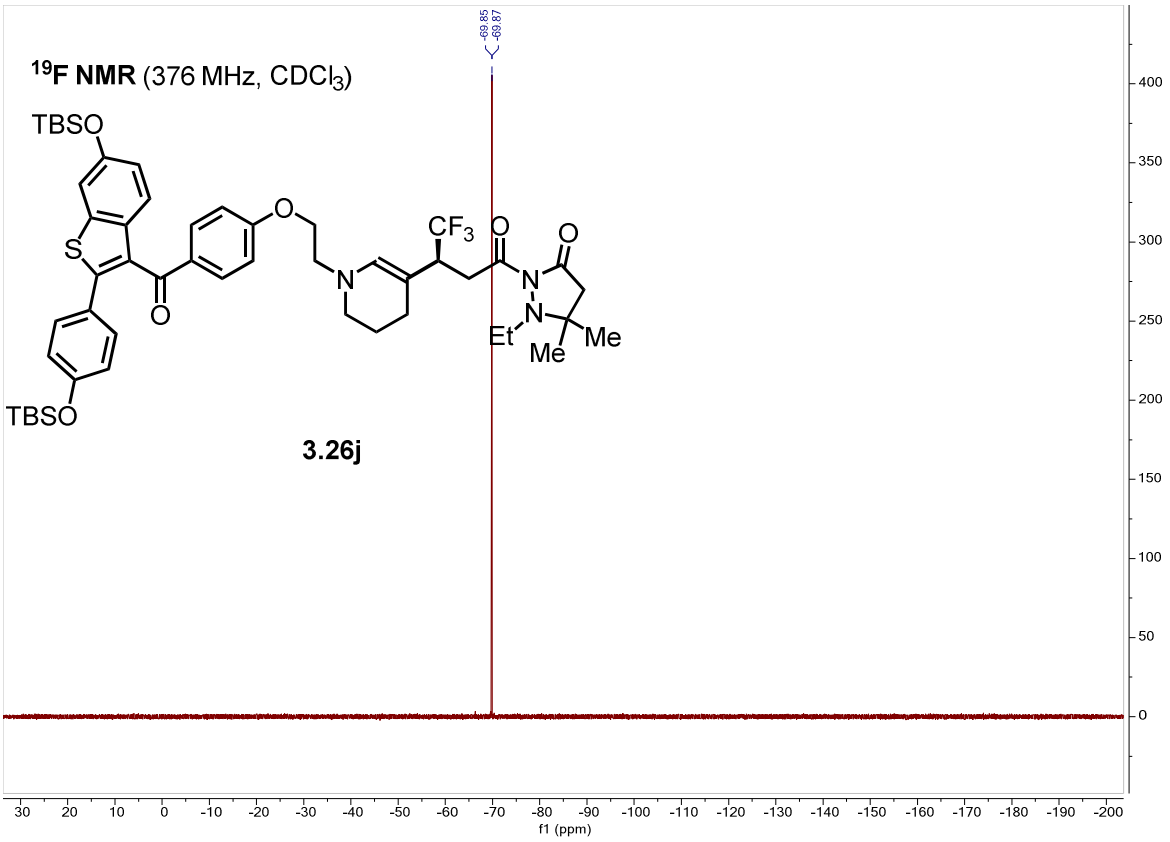

^{1}H NMR (400 MHz, $CDCl_3$)
3.26i
f1 (ppm)

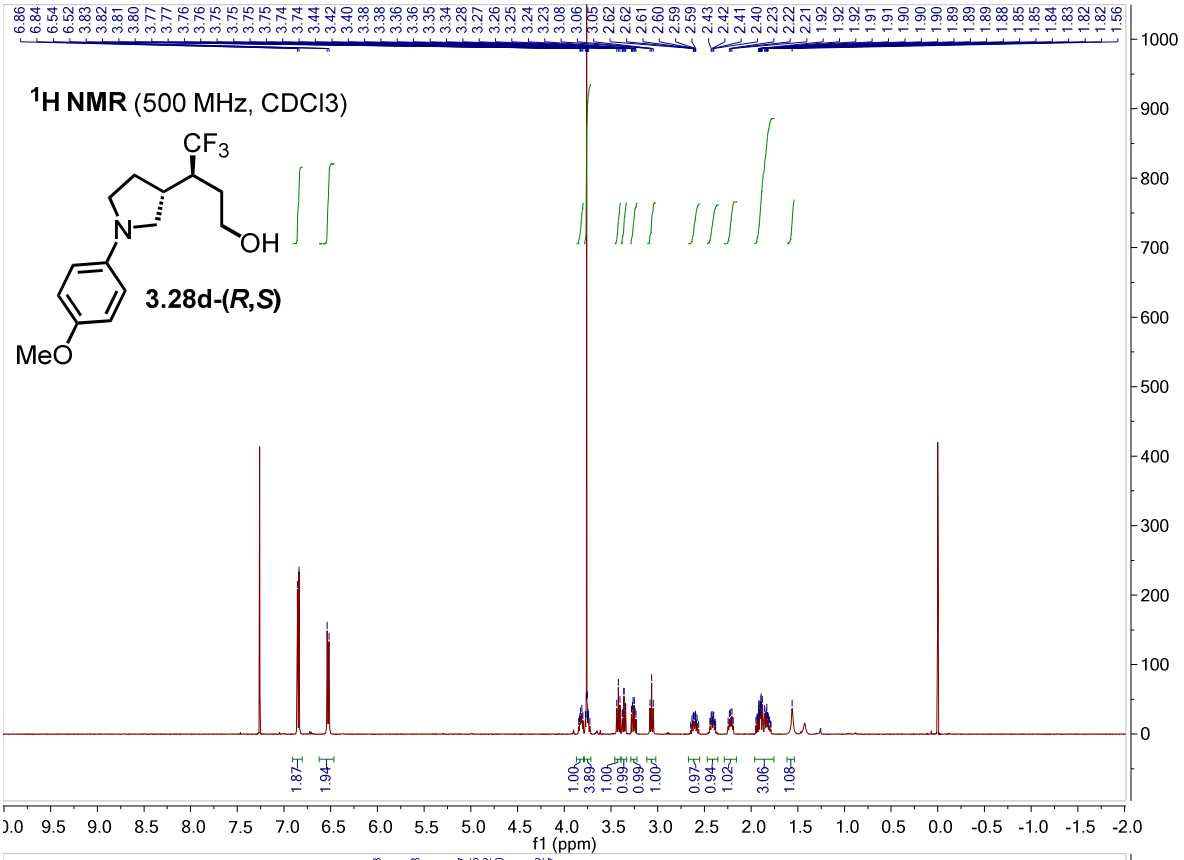

^{13}C NMR (126 MHz, $CDCl_3$)
3.26i
f1 (ppm)

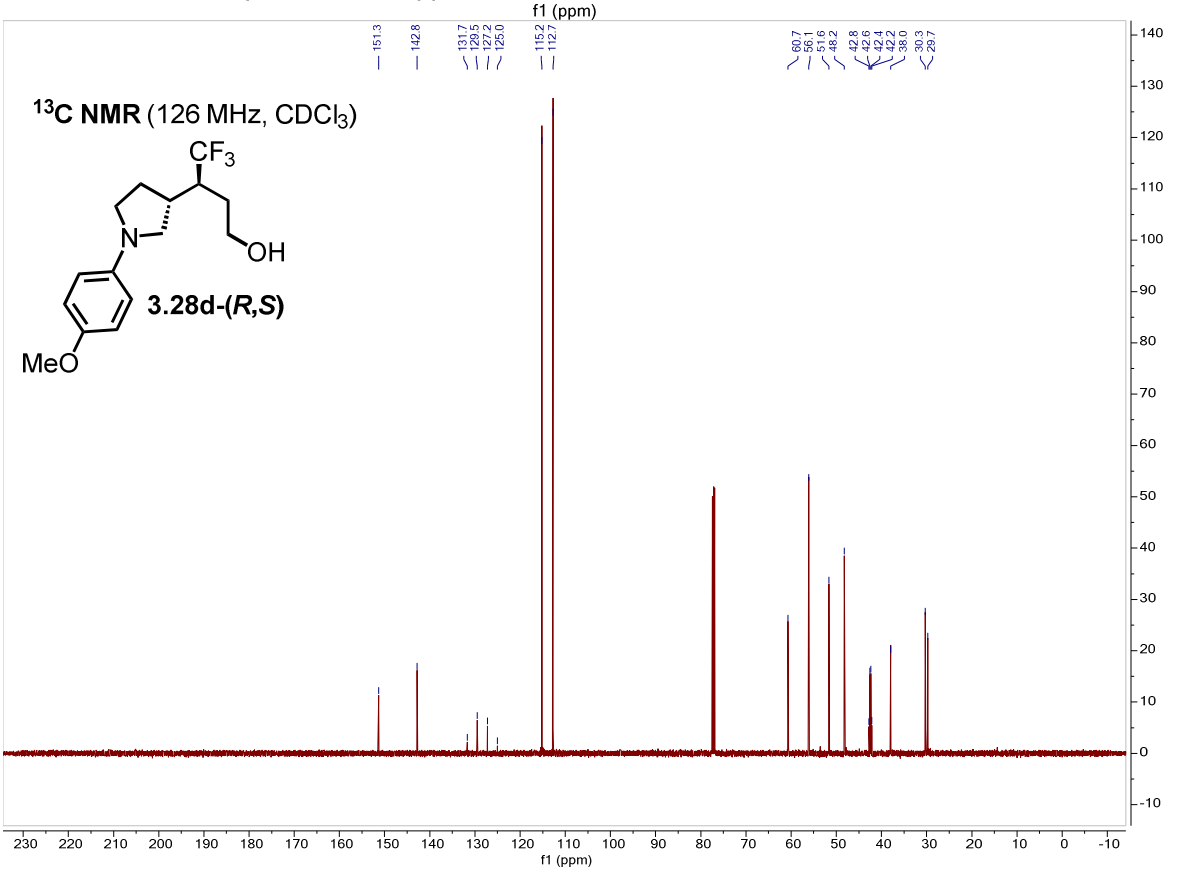

-69.77
-69.79
-69.81
19F NMR (470 MHz, CDCl3)
Cl
O
CF3
O
O
N
N
N
Et
Me
Me
3.26i
1000
900
800
700
600
500
400
300
200
100
0
-100
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

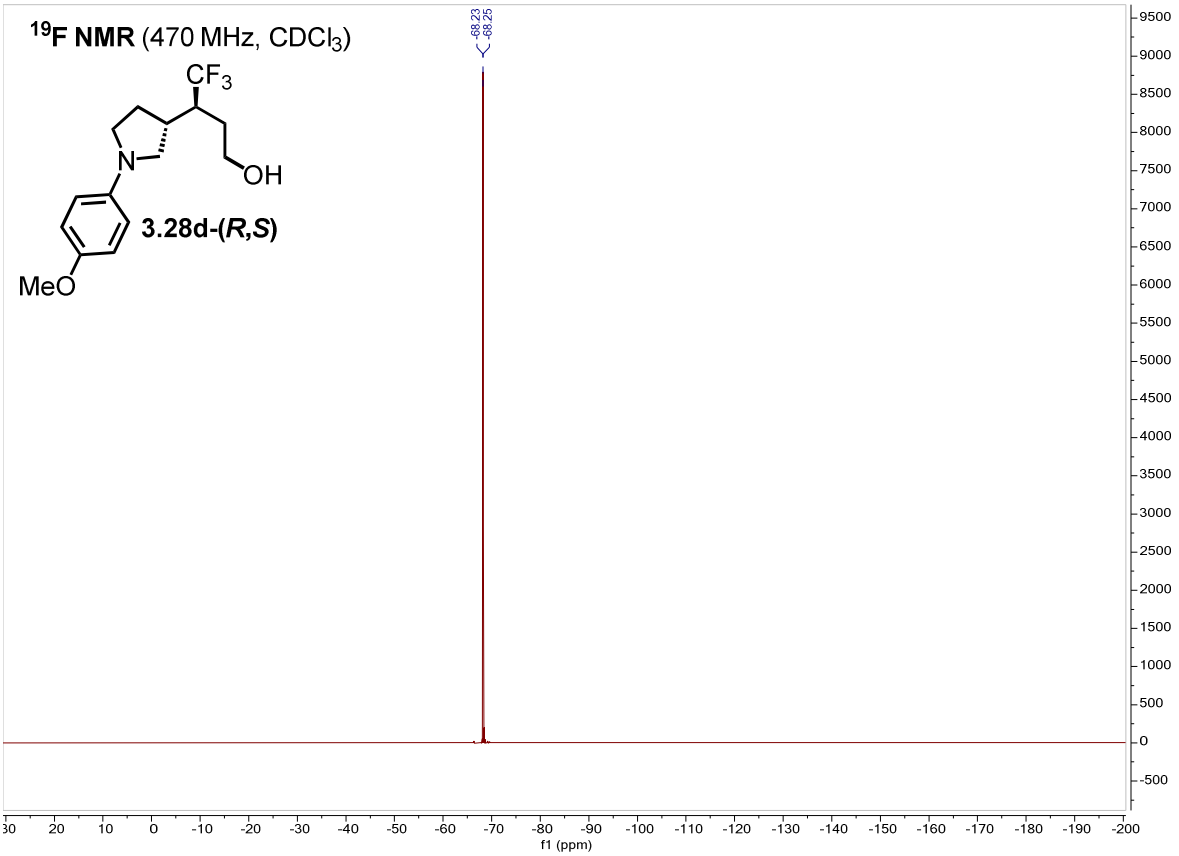

^{1}H NMR (500 MHz, $CDCl_3$)
TBSO
TBSO
CF_3
Et
Me
Me
3.26j
f1 (ppm)

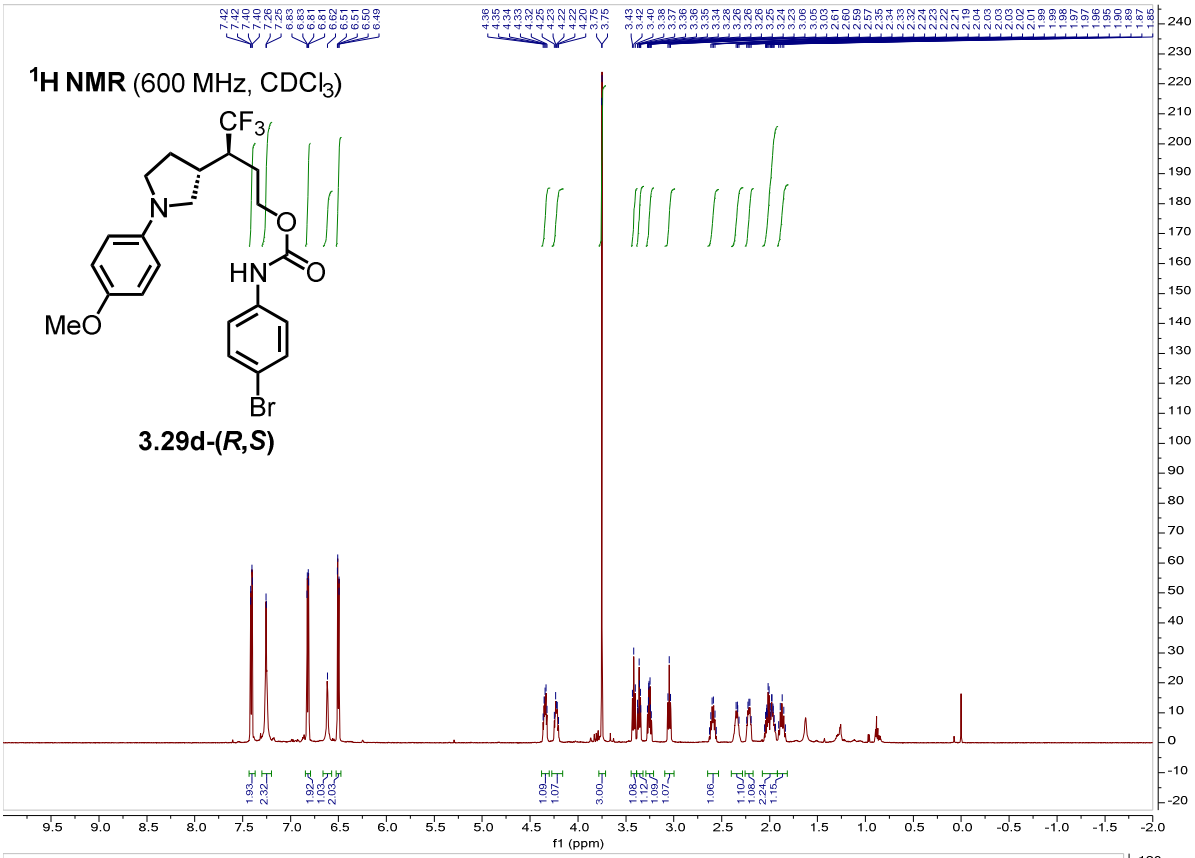

^{13}C NMR (101 MHz, $CDCl_3$)
TBSO
TBSO
CF_3
Et
Me
Me
3.26j
f1 (ppm)

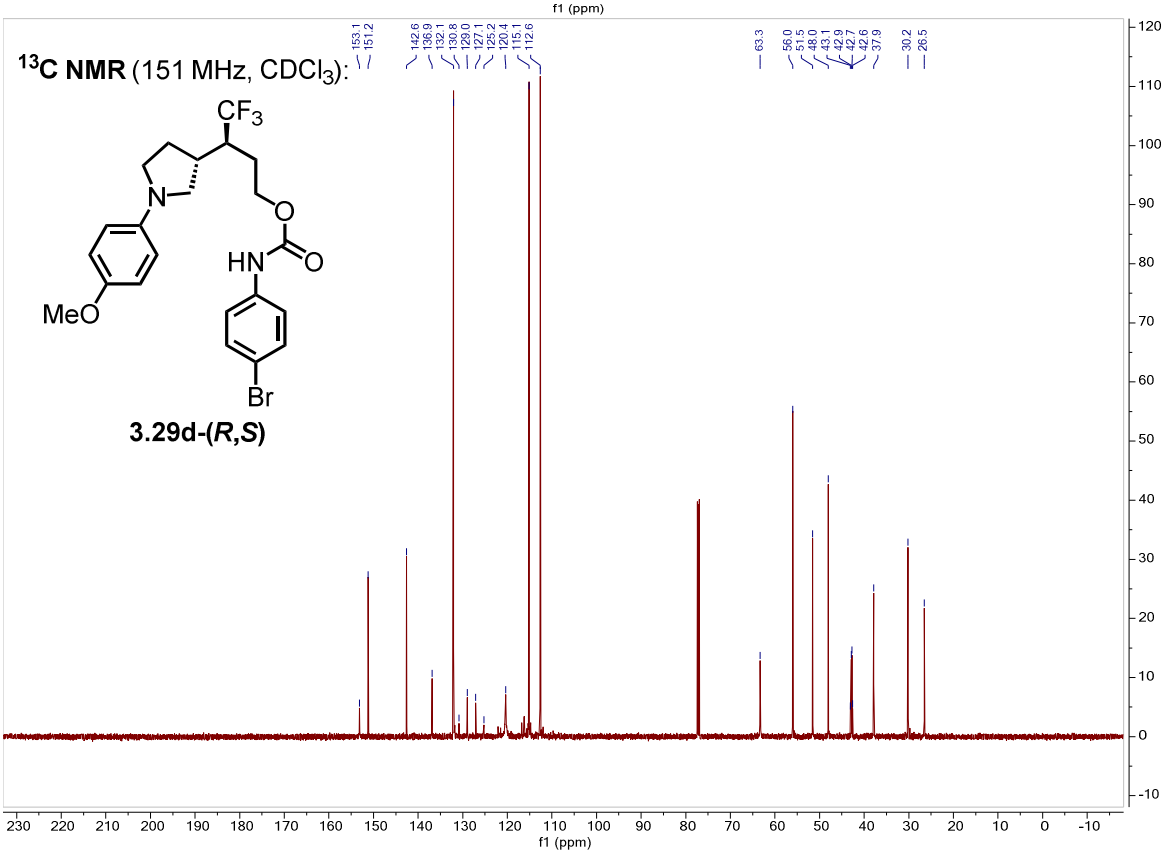

19F NMR (376 MHz, CDCl3)
TBSO
TBSO
S
O
O
N
CF3
O
N
N
O
Et
Me
Me
-69.85
-69.87
3.26j
400
350
300
250
200
150
100
50
0
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

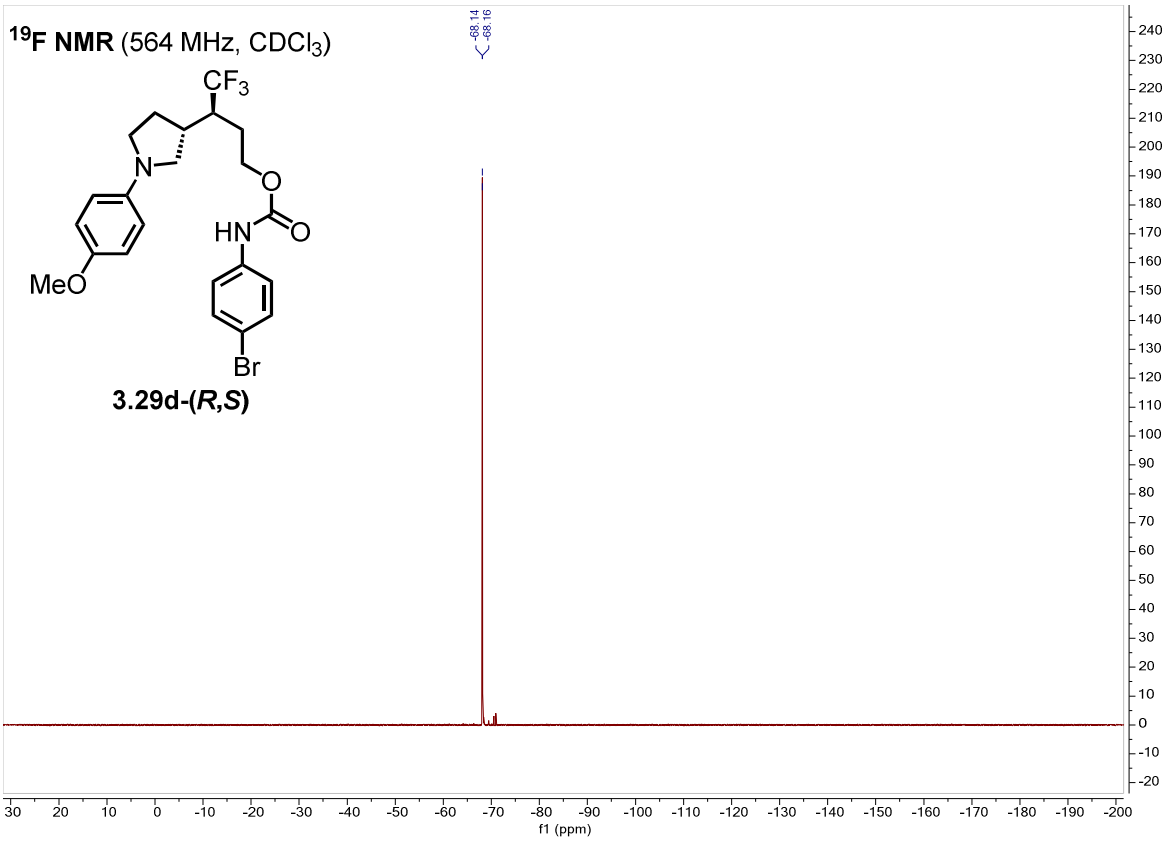

^{1}H NMR (500 MHz, CDCl3)
CF3
N
OH
MeO
3.28d-(R,S)
f1 (ppm)

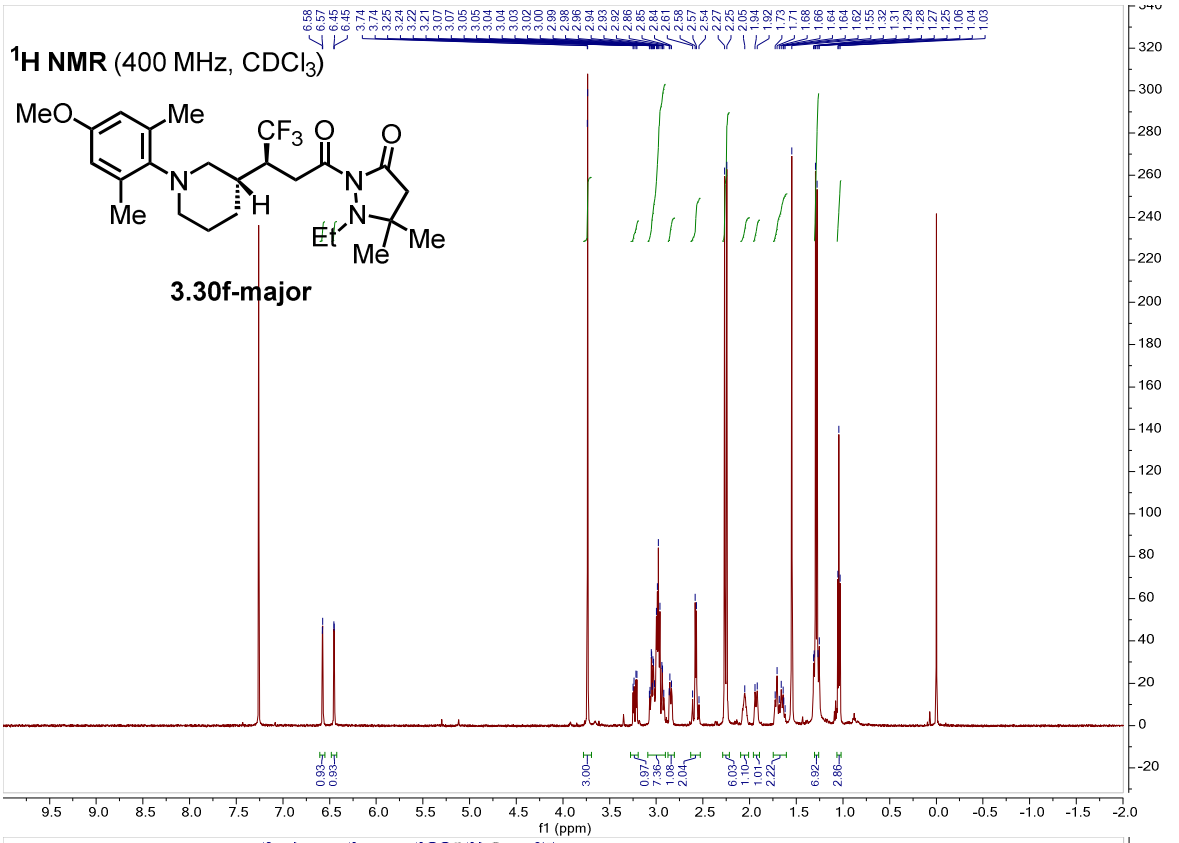

^{13}C NMR (126 MHz, CDCl$_3$)
CF3
N
OH
MeO
3.28d-(R,S)
f1 (ppm)

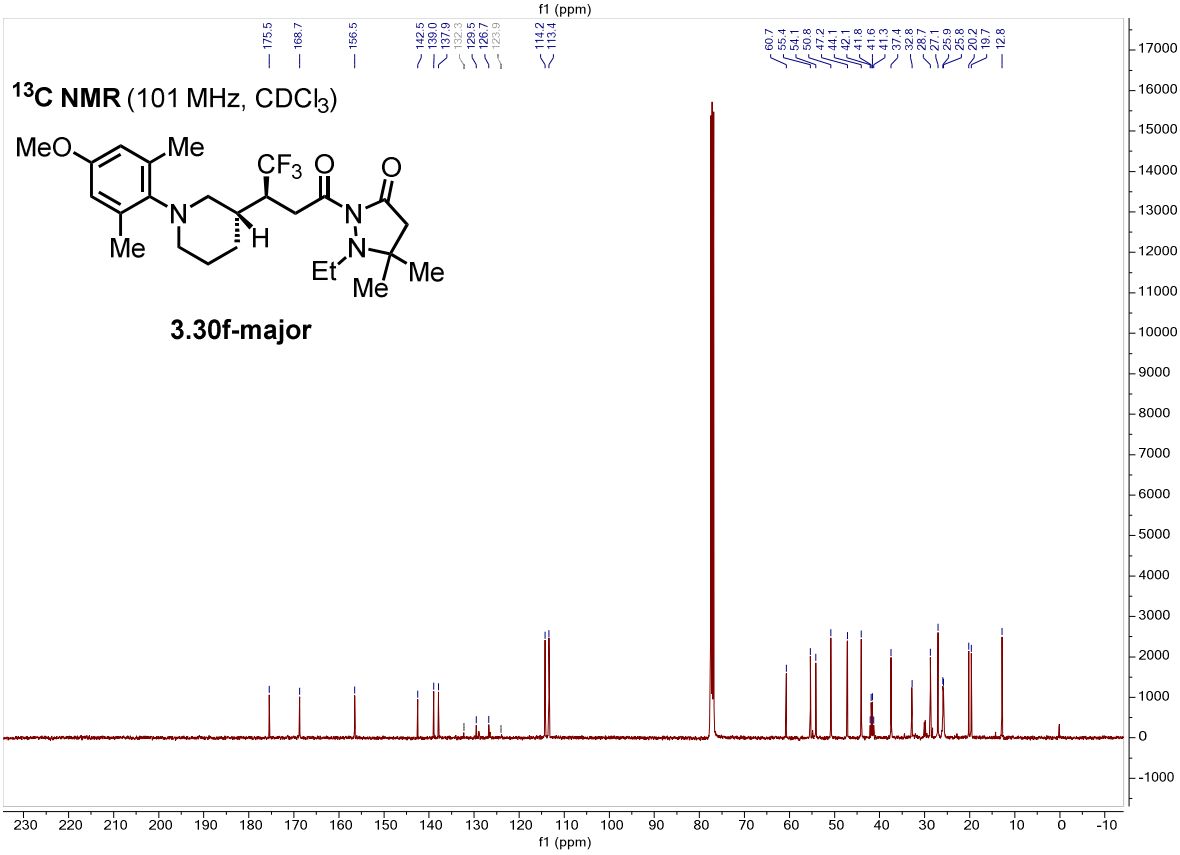

19F NMR (470 MHz, CDCl3)
CF3
N
OH
3.28d-(R,S)
MeO
-68.23
-68.25
f1 (ppm)

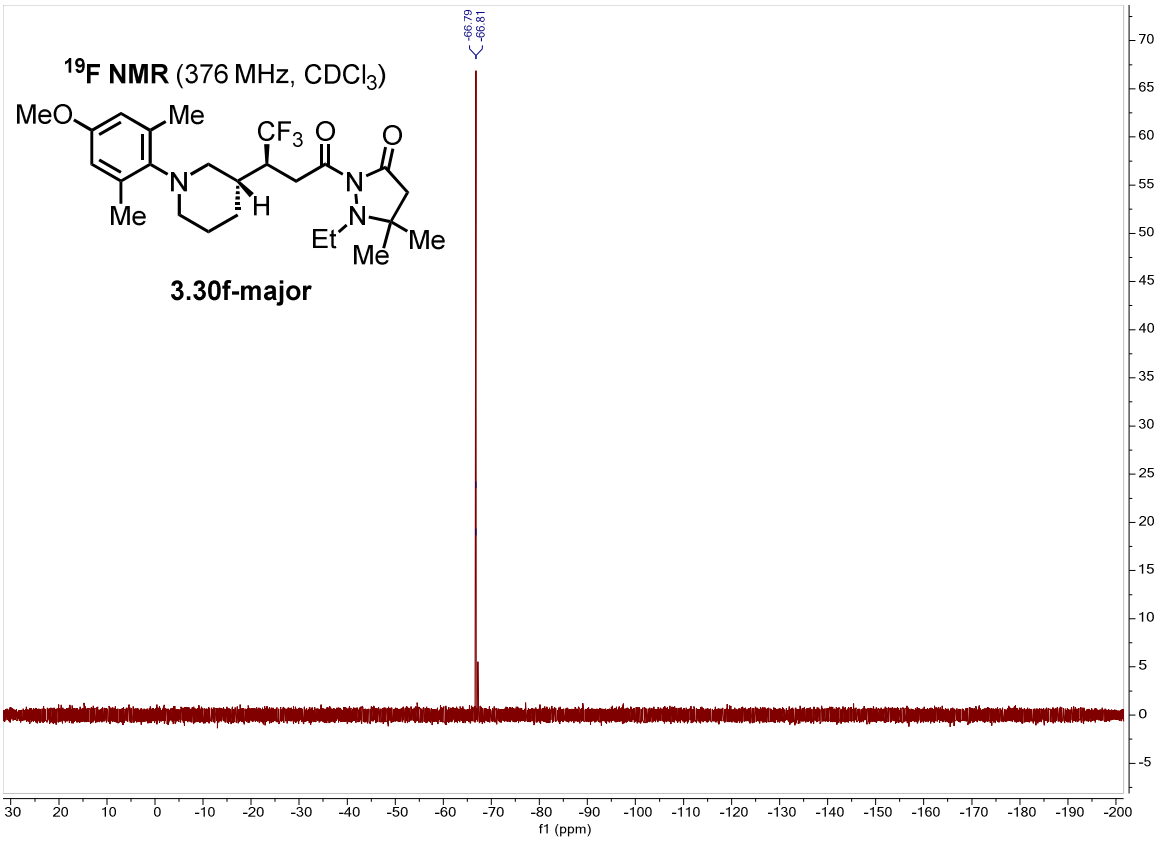

1H NMR (600 MHz, CDCl3)
CF3
N
O
HN
O
MeO
Br
3.29d-(R,S)
f1 (ppm)

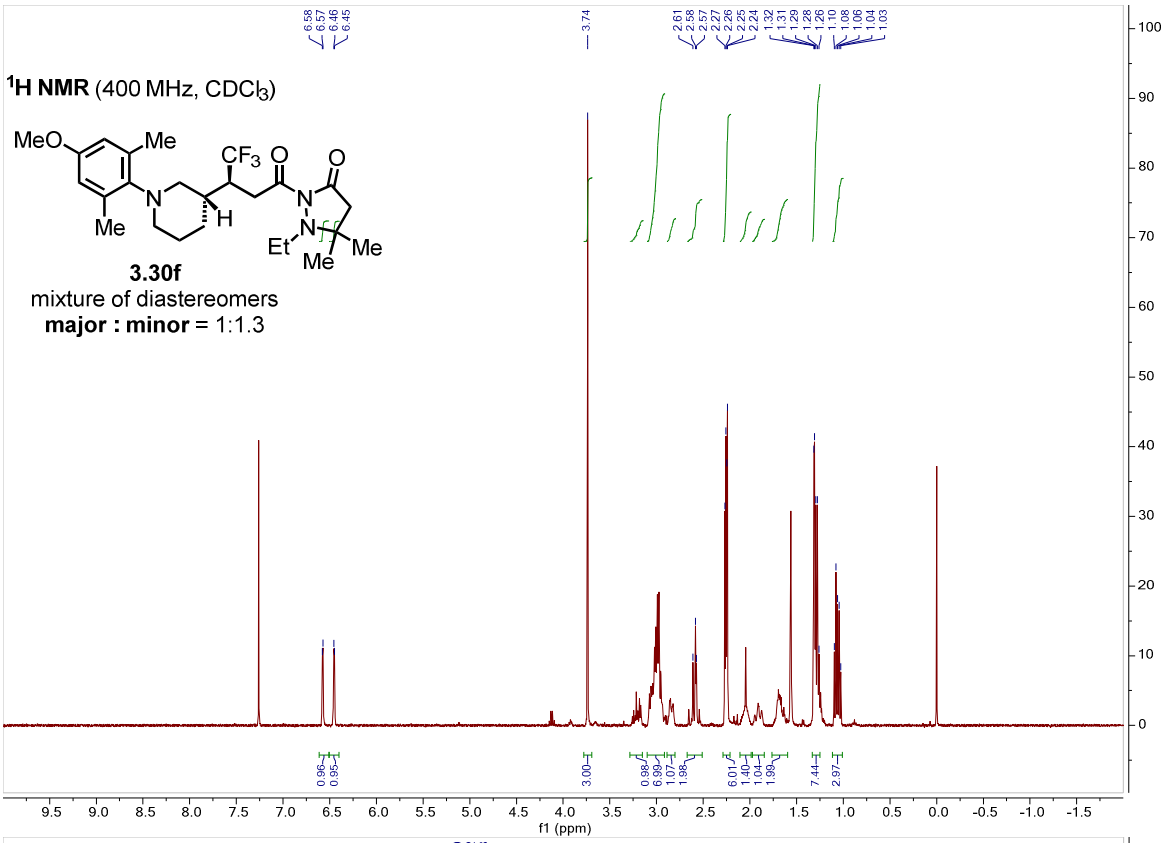

13C NMR (151 MHz, CDCl3):
CF3
N
O
HN
O
MeO
Br
3.29d-(R,S)
f1 (ppm)

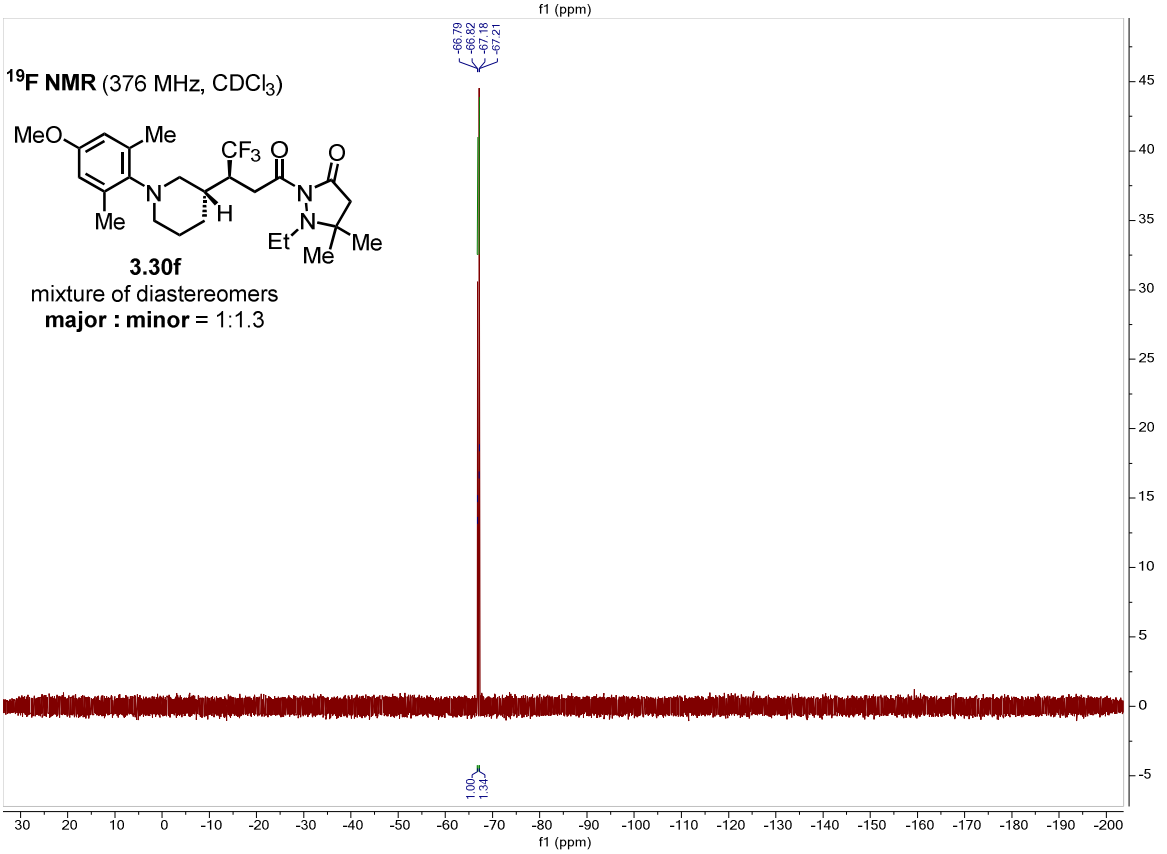

19F NMR (564 MHz, CDCl3)
CF3
N
O
HN
O
MeO
Br
3.29d-(R,S)
-68.14
-68.16
f1 (ppm)

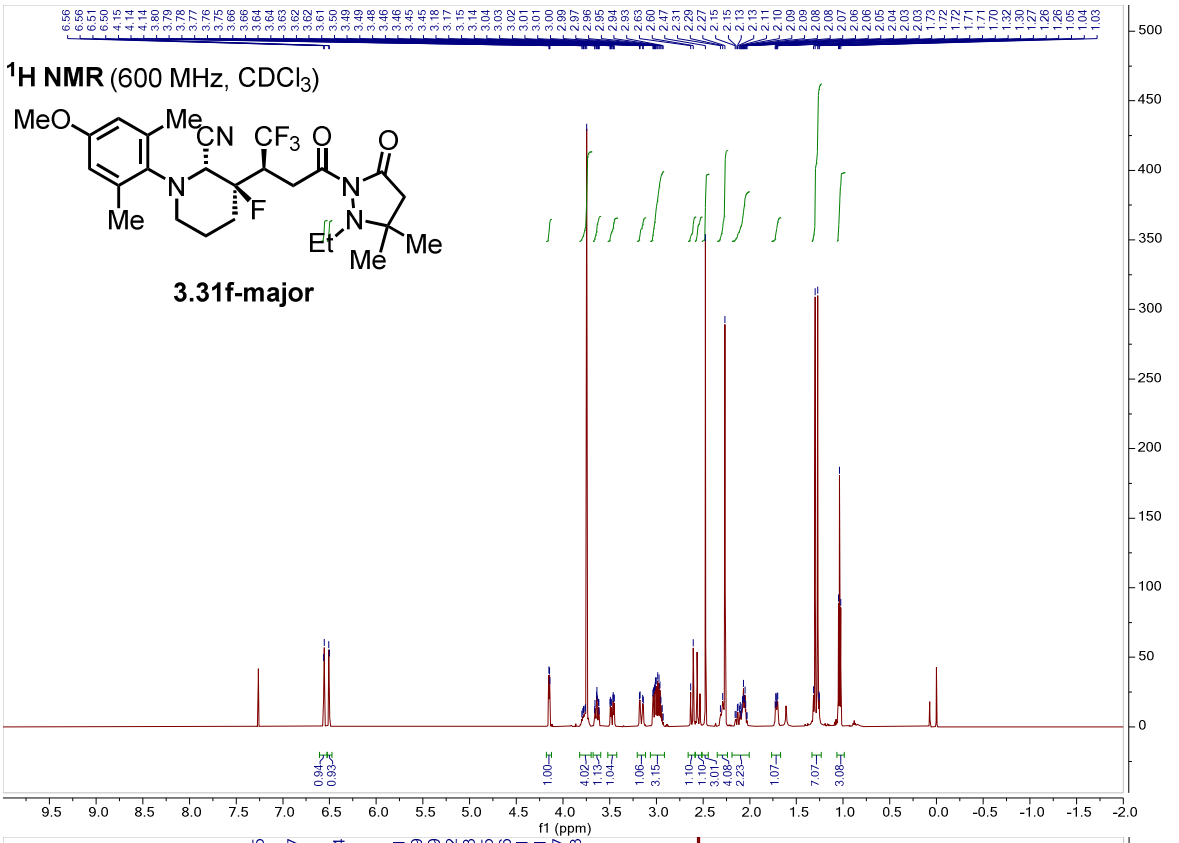

^{1}H NMR (400 MHz, CDCl$_3$)
MeO
Me
CF$_3$
O
O
N
N
H
Me
Et
N
Me
Me
3.30f-major
f1 (ppm)

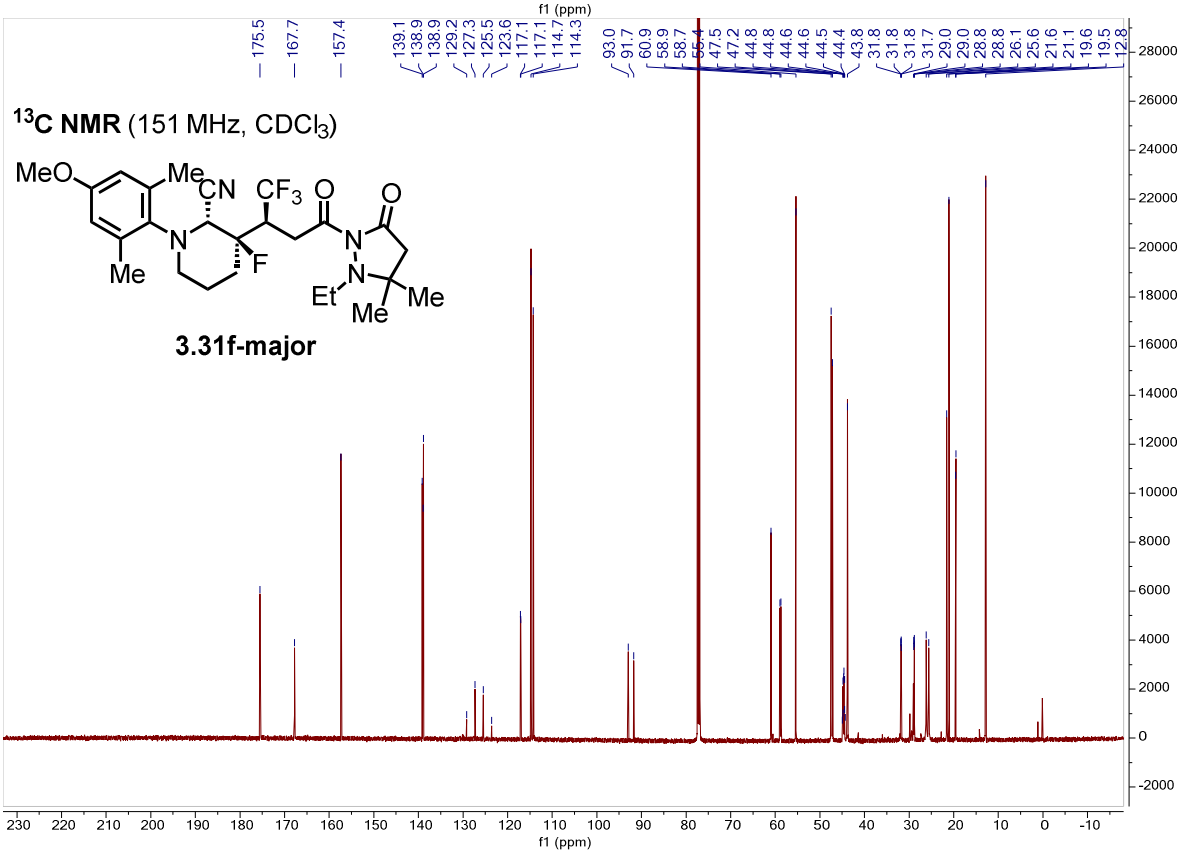

^{13}C NMR (101 MHz, CDCl$_3$)
MeO
Me
CF$_3$
O
O
N
N
H
Me
Et
N
Me
Me
3.30f-major
f1 (ppm)


19F NMR (376 MHz, CDCl3)
MeO
Me
CF3
O
O
N
N
N
H
Et
Me
Me
Me
3.30f-major
-66.79
-66.81
f1 (ppm)

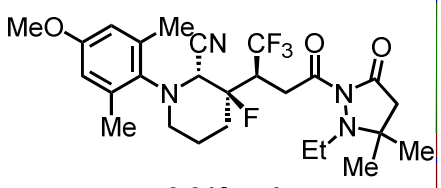

1H NMR (400 MHz, CDCl3)
MeO
Me
CF3
O
O
N
N
N
H
Et
Me
Me
Me
3.30f
mixture of diastereomers
major : minor = 1:1.3
f1 (ppm)


19F NMR (376 MHz, CDCl3)
MeO
Me
CF3
O
O
N
N
N
H
Et
Me
Me
Me
3.30f
mixture of diastereomers
major : minor = 1:1.3
f1 (ppm)


1H NMR (600 MHz, CDCl3)
3.31f-major
f1 (ppm)

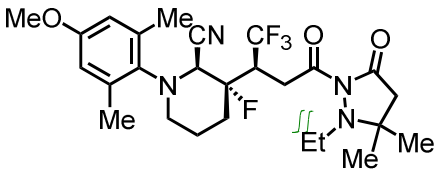

13C NMR (151 MHz, CDCl3)
3.31f-major
f1 (ppm)

^{19}F NMR (564 MHz, $CDCl_3$):

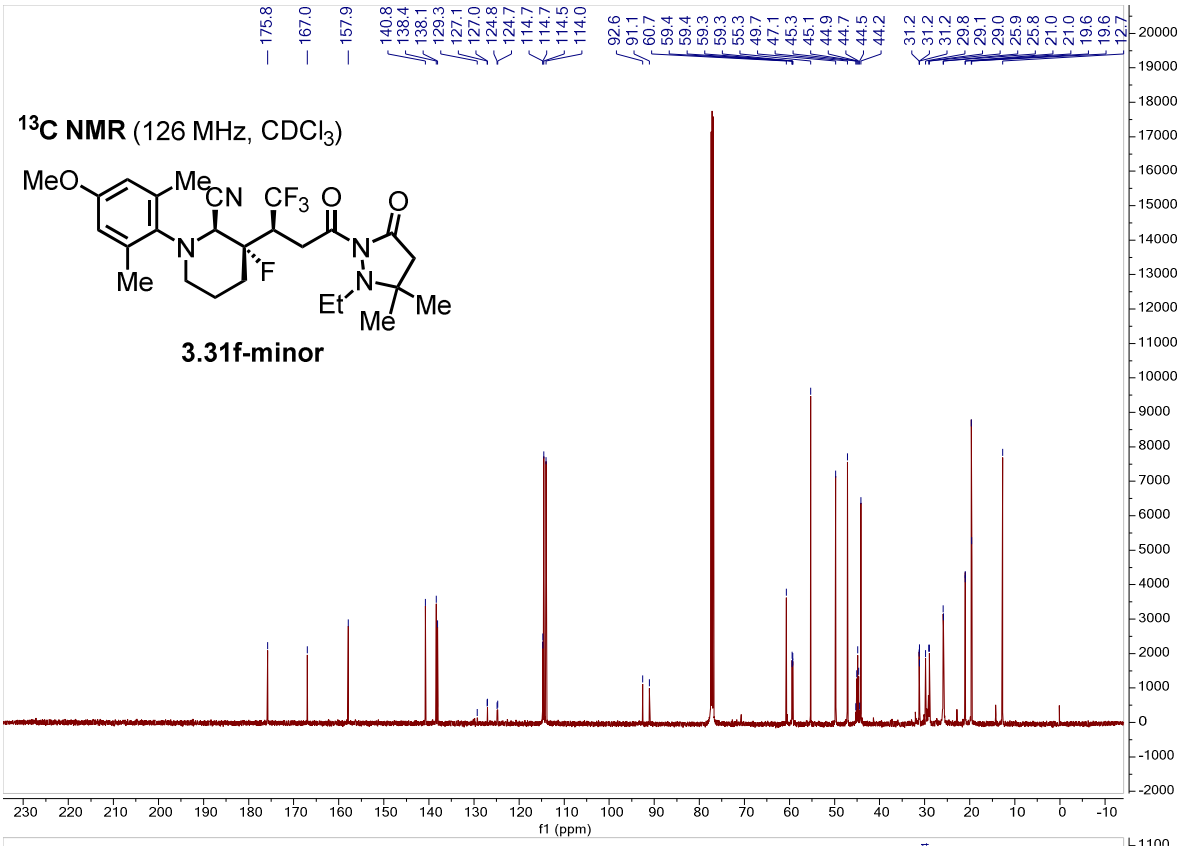


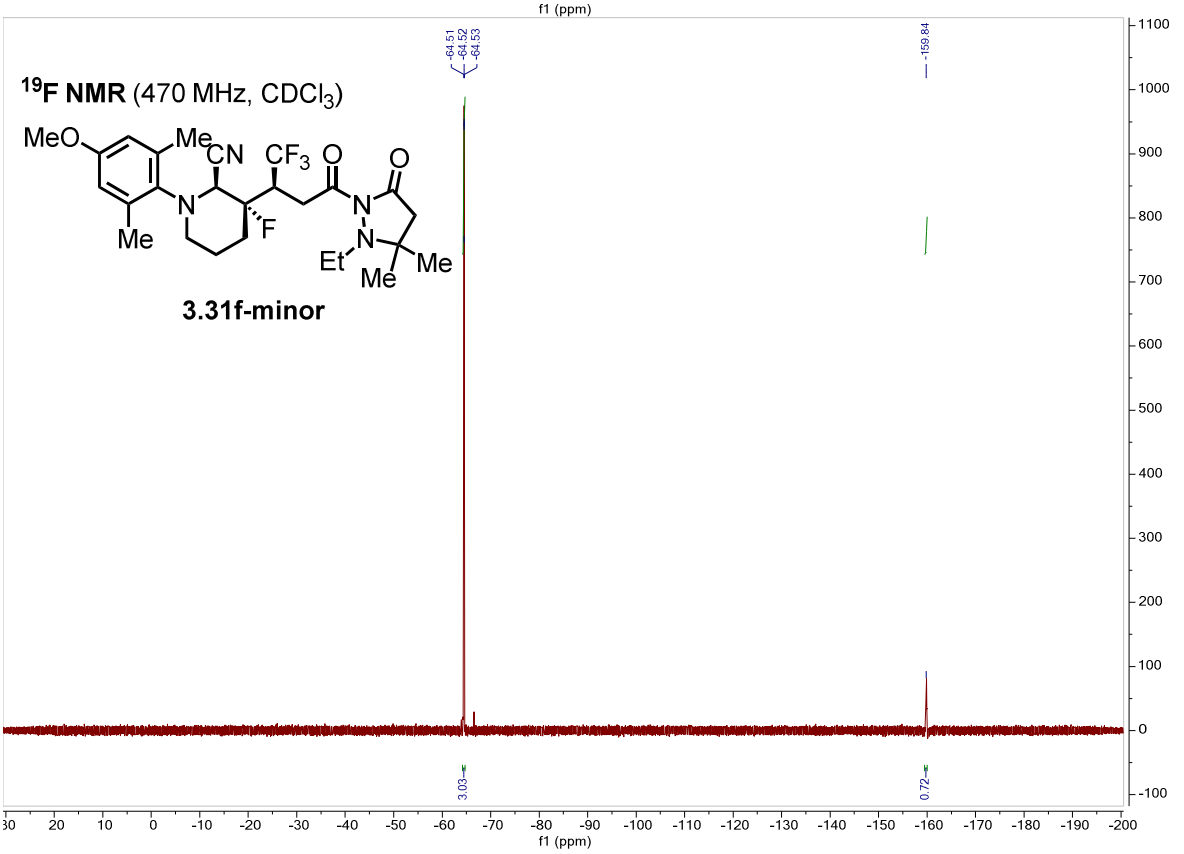
3.31f-major

^{1}H NMR (400 MHz, $CDCl_3$)



3.31f-minor


175.8
167.0
157.9
140.8
138.4
138.1
129.3
127.1
127.0
124.8
124.7
114.7
114.7
114.5
114.0
92.6
91.1
60.7
59.4
59.4
59.3
59.3
55.3
49.7
47.1
45.3
45.1
44.9
44.7
44.5
44.2
31.2
31.2
31.2
29.8
29.1
29.0
25.9
25.8
21.0
21.0
19.6
12.7
13C NMR (126 MHz, CDCl3)
MeO
Me
CN
CF3
O
O
N
N
F
Me
Et
N
Me
Me
3.31f-minor
f1 (ppm)


-64.51
-64.52
-64.53
-159.84
19F NMR (470 MHz, CDCl3)
MeO
Me
CN
CF3
O
O
N
N
F
Me
Et
N
Me
Me
3.31f-minor
3.03
0.72
f1 (ppm)

3.6.9. X-Ray Crystallography Data

3.6.9.1. X-Ray Crystallography Data of 3.21e-major

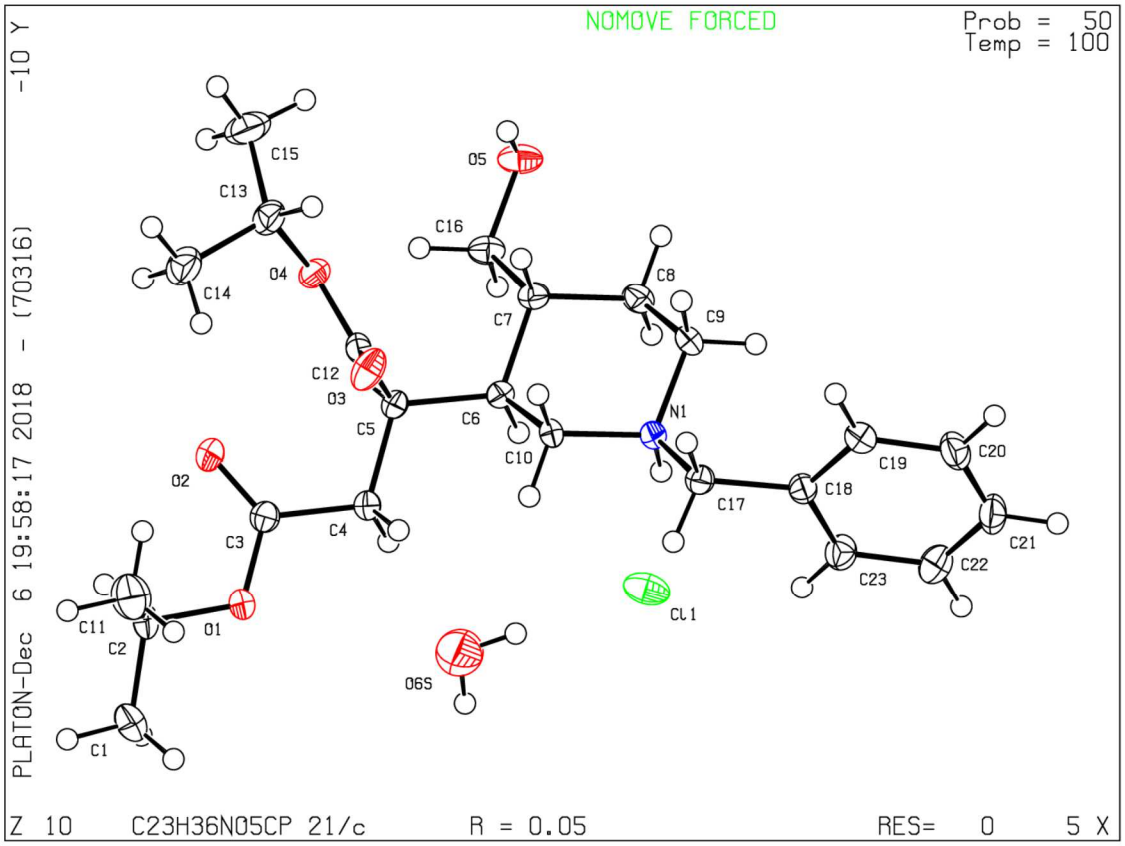


Table S7. Crystal data and structure refinement for $C_{23}H_{36}NO_5$+Cl-.

Identification code	C23H36NO5+Cl-	
Empirical formula	C23 H37 Cl N O5.50	
Formula weight	450.98	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 15.0369(10) Å	α= 90°.
	b = 15.1361(9) Å	β= 109.486(2)°.
	c = 11.4130(7) Å	γ = 90°.
Volume	2448.8(3) $Å^3$	
Z	4	
Density (calculated)	1.223 Mg/m^3	
Absorption coefficient	1.662 mm^{-1}	
F(000)	972	
Crystal size	0.570 x 0.250 x 0.220 mm^3	
Theta range for data collection	4.273 to 66.688°.	
Index ranges	-17<=h<=17, -17<=k<=18, -13<=l<=13	
Reflections collected	26897	
Independent reflections	4324 [R(int) = 0.0346]	
Completeness to theta = 66.688°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7528 and 0.5887	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4324 / 4 / 296	
Goodness-of-fit on F^2	1.145	
Final R indices [I>2sigma(I)]	R1 = 0.0506, wR2 = 0.1303	
R indices (all data)	R1 = 0.0511, wR2 = 0.1306	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.409 and -0.389 $e.Å^{-3}$	

3.6.9.2. X-Ray Crystallography Data of 3.21e-Minor

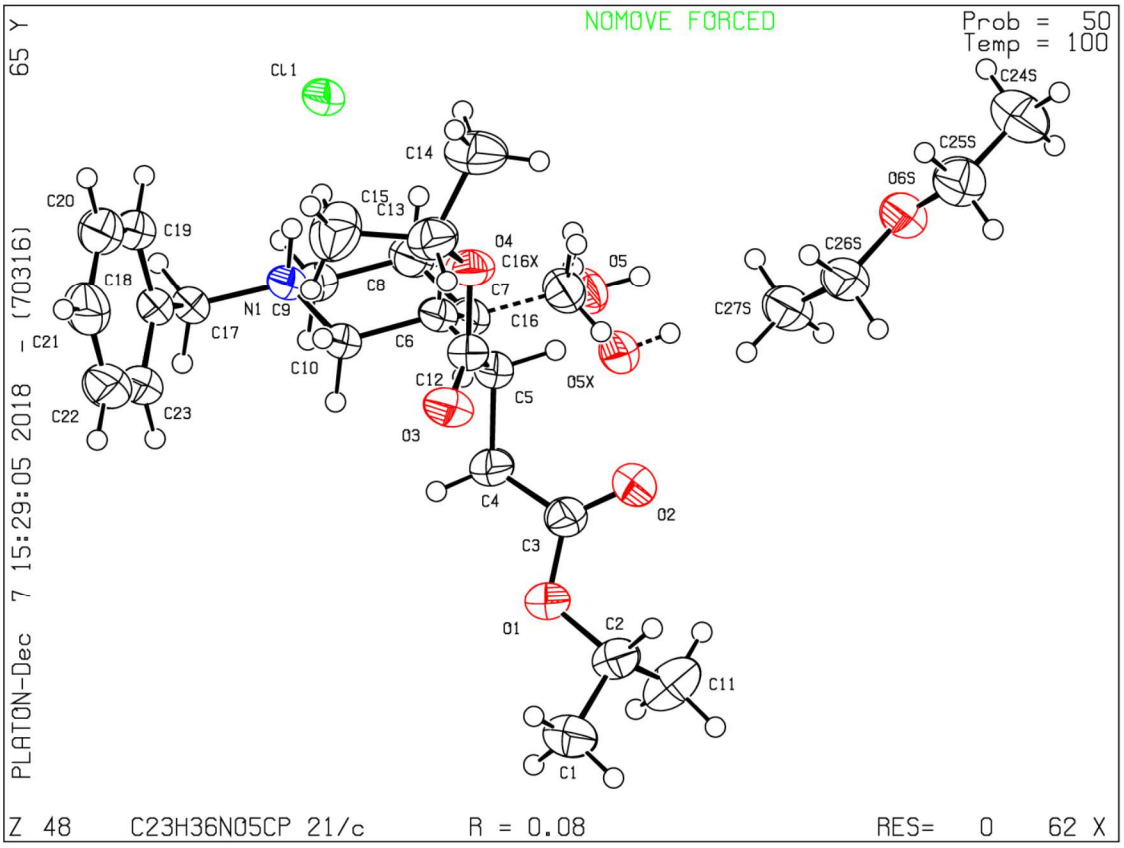


Table S8. Crystal data and structure refinement for $C_{23}H_{36}NO_5$+Cl-.

Identification code	(C23H36NO5)+Cl-	
Empirical formula	C27 H46 Cl N O6	
Formula weight	516.10	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 12.7945(13) Å	a= 90°.
	b = 16.9523(16) Å	b= 90.019(5)°.
	c = 13.6116(13) Å	g = 90°.
Volume	2952.3(5) $Å^3$	
Z	4	
Density (calculated)	1.161 Mg/m^3	
Absorption coefficient	1.449 mm^{-1}	
F(000)	1120	
Crystal size	0.600 x 0.280 x 0.220 mm^3	
Theta range for data collection	3.454 to 66.915°.	
Index ranges	-15<=h<=15, -20<=k<=0, -16<=l<=16	
Reflections collected	9581	
Independent reflections	5139 [R(int) = 0.0569]	
Completeness to theta = 66.915°	97.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7528 and 0.5470	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5139 / 1 / 335	
Goodness-of-fit on F2	1.065	
Final R indices [I>2sigma(I)]	R1 = 0.0789, wR2 = 0.2343	
R indices (all data)	R1 = 0.0836, wR2 = 0.2389	
Extinction coefficient	n/a	
Largest diff. peak and hole	1.050 and -0.299 $e.Å^{-3}$	

3.6.9.3. X-Ray Crystallography Data of 3.34b-Major

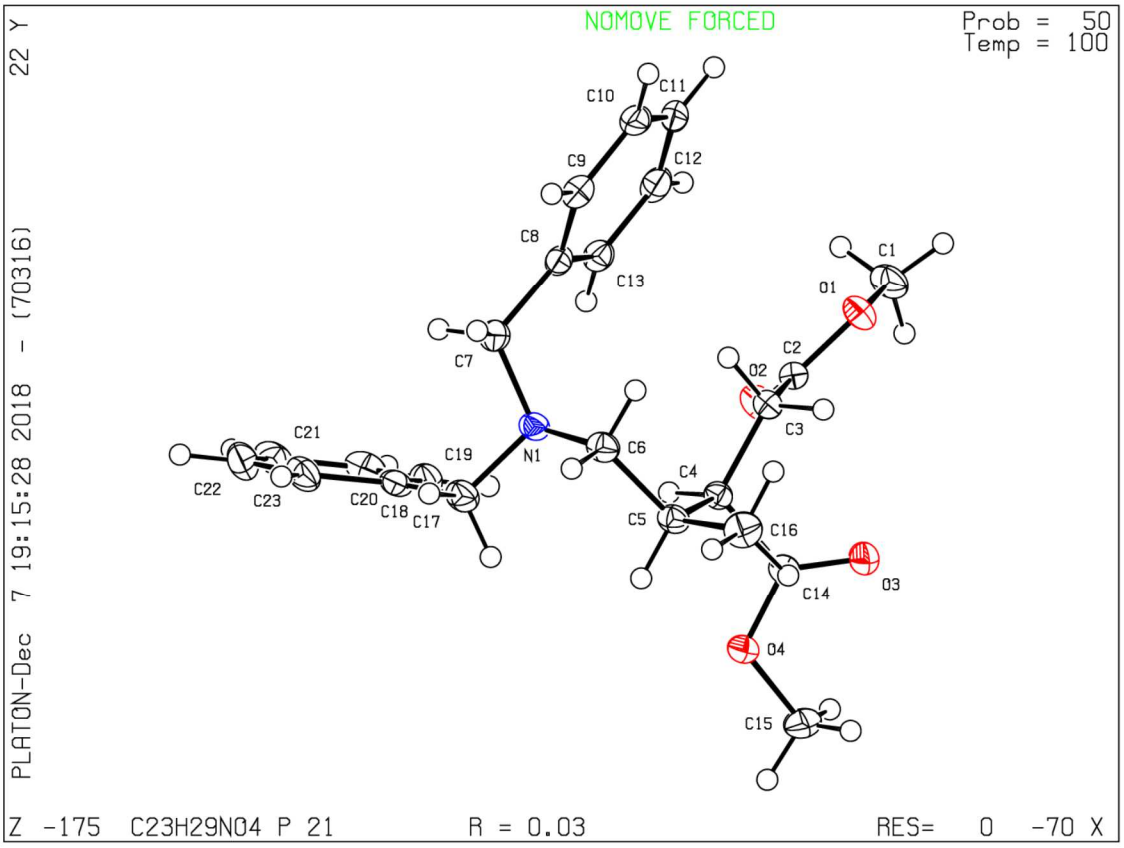


Table S9. Crystal data and structure refinement for $C_{23}H_{29}NO_4$.

Identification code	C23H29NO4	
Empirical formula	C23 H29 N O4	
Formula weight	383.47	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 10.2867(8) Å	α= 90°.
	b = 7.8024(7) Å	β= 94.248(4)°.
	c = 13.1792(10) Å	γ = 90°.
Volume	1054.87(15) $Å^3$	
Z	2	
Density (calculated)	1.207 Mg/m^3	
Absorption coefficient	0.659 mm^{-1}	
F(000)	412	
Crystal size	0.600 x 0.320 x 0.220 mm^3	
Theta range for data collection	3.363 to 66.626°.	
Index ranges	-9<=h<=12, -9<=k<=7, -15<=l<=15	
Reflections collected	6116	
Independent reflections	2950 [R(int) = 0.0250]	
Completeness to theta = 66.626°	99.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7528 and 0.5979	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2950 / 1 / 255	
Goodness-of-fit on F^2	1.076	
Final R indices [I>2sigma(I)]	R1 = 0.0275, wR2 = 0.0732	
R indices (all data)	R1 = 0.0276, wR2 = 0.0734	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.170 and -0.145 $e.Å^{-3}$	

3.6.9.4. X-Ray Crystallography Data of 3.34q-Major

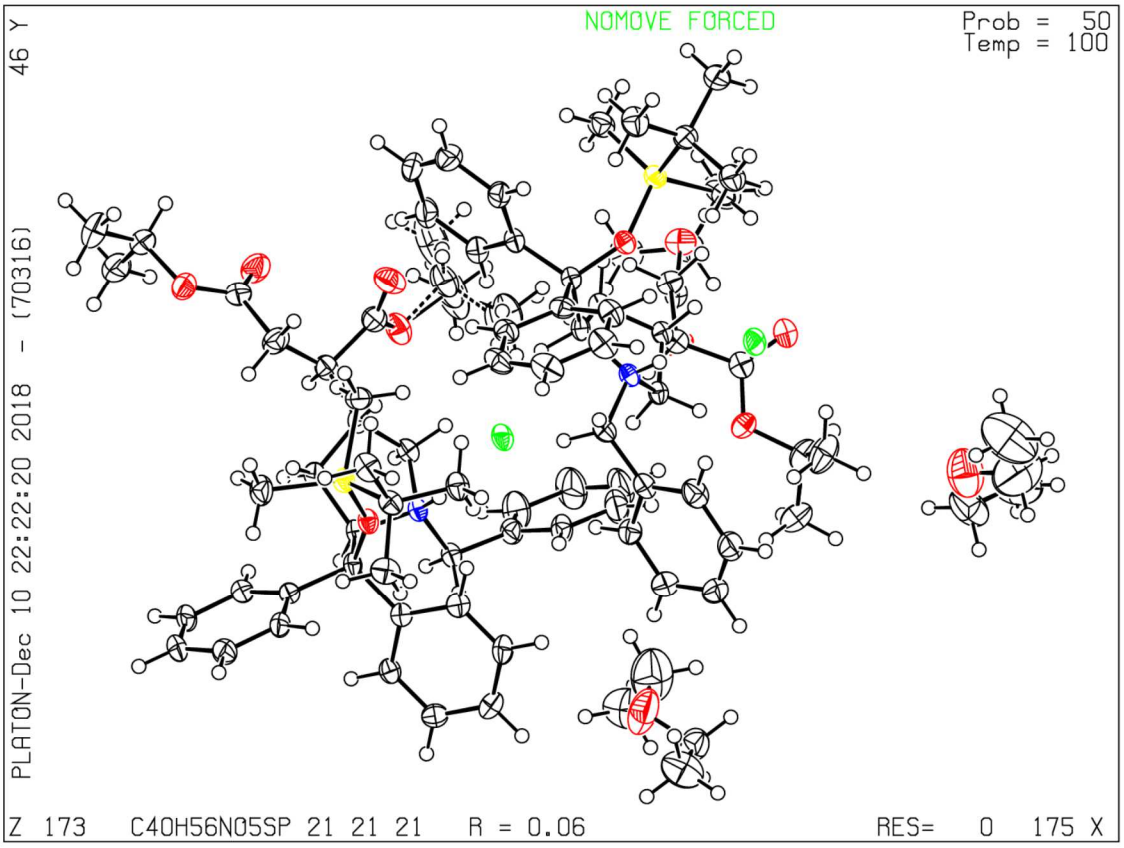


Table S10. Crystal data and structure refinement for $(C_{40}H_{56}NO_5Si)+Cl-$

Identification code	(C40H56NO5Si)+Cl-	
Empirical formula	C44 H66 Cl N O6 Si	
Formula weight	768.51	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 13.8219(7) Å	α= 90°.
	b = 25.0250(14) Å	β= 90°.
	c = 26.0978(14) Å	γ = 90°.
Volume	9027.0(8) $Å^3$	
Z	8	
Density (calculated)	1.131 Mg/m^3	
Absorption coefficient	1.348 mm^{-1}	
F(000)	3328	
Crystal size	0.540 x 0.100 x 0.080 mm^3	
Theta range for data collection	2.446 to 66.712°.	
Index ranges	-15<=h<=16, -29<=k<=29, -31<=l<=25	
Reflections collected	46423	
Independent reflections	15586 [R(int) = 0.0733]	
Completeness to theta = 66.712°	99.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7528 and 0.5629	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	15586 / 793 / 965	
Goodness-of-fit on F^2	1.050	
Final R indices [I>2sigma(I)]	R1 = 0.0642, wR2 = 0.1605	
R indices (all data)	R1 = 0.0698, wR2 = 0.1646	
Absolute structure parameter	0.037(7)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.742 and -0.534 $e.Å^{-3}$	

3.6.9.5. X-Ray Crystallography Data of 3.35b

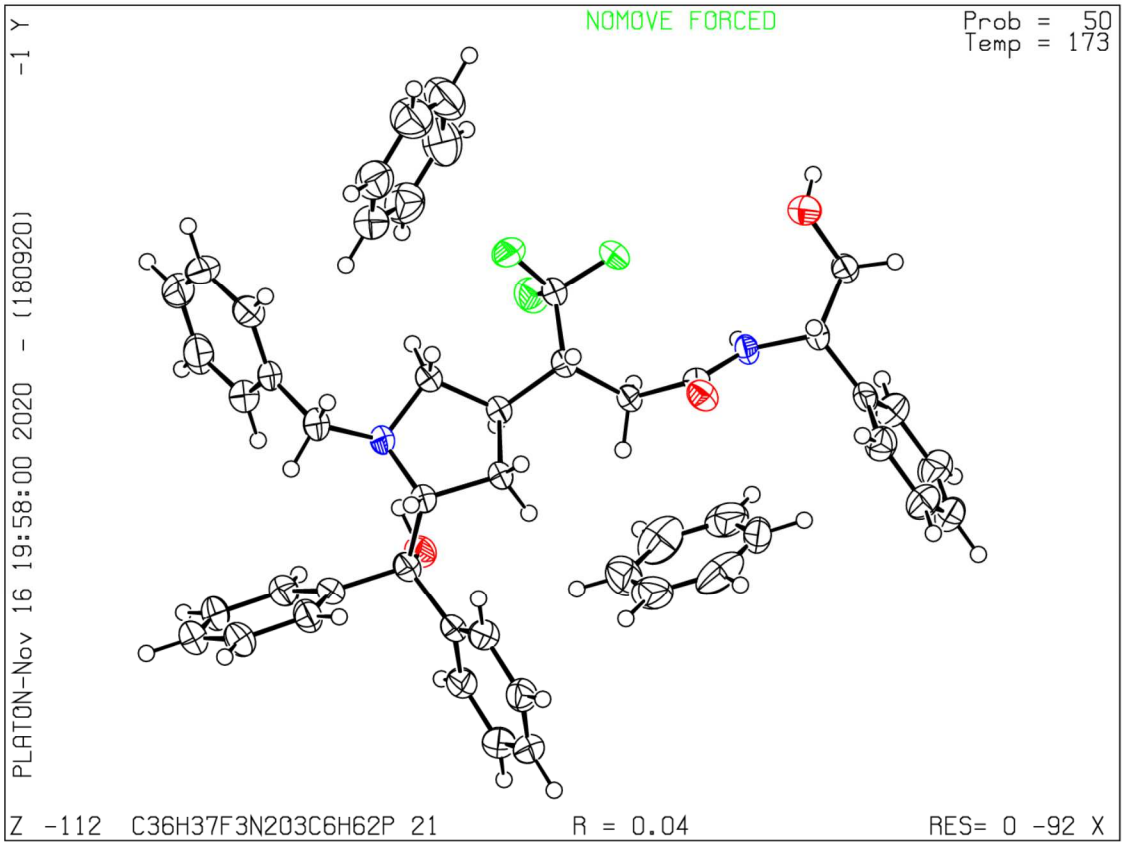


Table S11. Crystal data and structure refinement for $C_{36}H_{37}F_3N_2O_3(C_6H_6)_2$.

Identification code	C36H37F3N2O3(C6H6)2	
Empirical formula	C48 H49 F3 N2 O3	
Formula weight	758.89	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 13.7584(15) Å	α= 90°.
	b = 6.1841(7) Å	β= 100.009(6)°.
	c = 24.281(3) Å	γ = 90°.
Volume	2034.4(4) $Å^3$	
Z	2	
Density (calculated)	1.239 Mg/m^3	
Absorption coefficient	0.698 mm^{-1}	
F(000)	804	
Crystal size	0.360 x 0.180 x 0.120 mm^3	
Theta range for data collection	1.848 to 67.096°.	
Index ranges	-16<=h<=16, -7<=k<=7, -28<=l<=28	
Reflections collected	52023	
Independent reflections	7082 [R(int) = 0.0633]	
Completeness to theta = 67.096°	98.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7528 and 0.6627	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7082 / 33 / 514	
Goodness-of-fit on F^2	1.061	
Final R indices [I>2sigma(I)]	R1 = 0.0399, wR2 = 0.0896	
R indices (all data)	R1 = 0.0503, wR2 = 0.0949	
Absolute structure parameter	-0.06(8)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.143 and -0.173 $e.Å^{-3}$	

3.6.9.6. X-Ray Crystallography Data of 3.29d

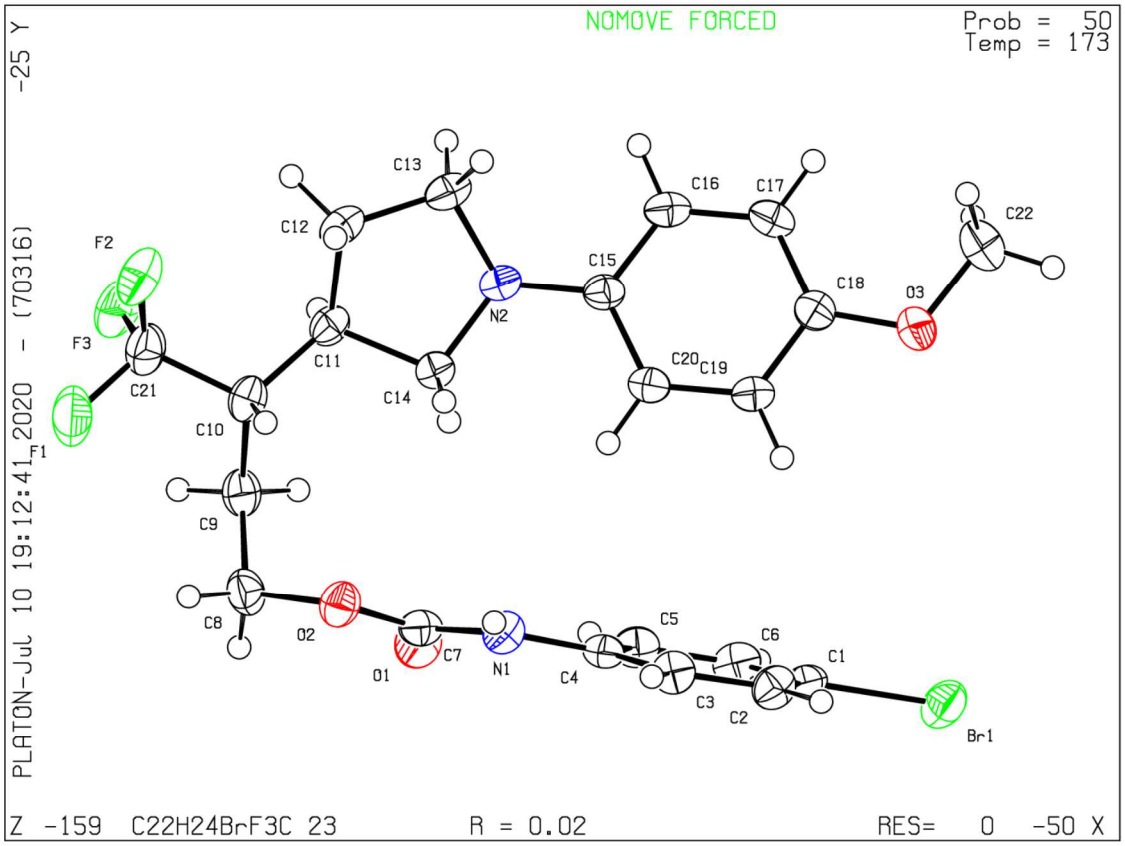


Table S12. Crystal data and structure refinement for $C_{22}H_{24}BrF_3N_2O_3$.

Identification code	C22H24BrF3N2O3	
Empirical formula	C22 H24 Br F3 N2 O3	
Formula weight	501.34	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 46.369(4) Å	α= 90°.
	b = 5.7157(5) Å	β= 91.434(2)°.
	c = 7.9867(7) Å	γ = 90°.
Volume	2116.0(3) Å^3	
Z	4	
Density (calculated)	1.574 Mg/m^3	
Absorption coefficient	3.128 mm^{-1}	
F(000)	1024	
Crystal size	0.560 x 0.380 x 0.160 mm^3	
Theta range for data collection	3.814 to 66.565°.	
Index ranges	-54<=h<=54, -6<=k<=6, -9<=l<=9	
Reflections collected	32823	
Independent reflections	3675 [R(int) = 0.0304]	
Completeness to theta = 66.565°	98.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7528 and 0.4622	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3675 / 1 / 280	
Goodness-of-fit on F^2	1.059	
Final R indices [I>2sigma(I)]	R1 = 0.0218, wR2 = 0.0587	
R indices (all data)	R1 = 0.0218, wR2 = 0.0587	
Absolute structure parameter	-0.007(7)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.388 and -0.506 e.Å^{-3}	